NATIONAL INSTITUTES OF HEALTH (NIH)

Office of the Director

SIGNIFICANT ITEMS IN HOUSE, SENATE AND CONFERENCE APPROPRIATION COMMITTEE REPORTS

FY 2005 House Appropriations Committee Report Language (H. Rpt 108-636)

Item

Office of Research on Women's Health – [Uterine fibroids] - Twenty to thirty percent of women in the U.S. of reproductive age suffer from uterine fibroids, a benign tumor that affects their reproductive health. Research on treatment has been limited, and often women have unnecessary hysterectomies when less costly and invasive treatments may be possible. In conjunction with National Institute of Child Health and Human Development (NICHD), National Institute of Environmental Health Sciences (NIEHS), and National Center on Minority Health and Health Disparities (NCMHD), ORWH is encouraged to intensify and coordinate programs to support research on uterine fibroids. (p.105)

Action taken or to be taken

NIH has a strong commitment to foster research on uterine fibroids, also referred to as leiomyomas, because of the prevalence of this condition and the health disparities that exist in certain populations of women. Based on results obtained using new molecular approaches, NICHD researchers report that uterine fibroids have reduced levels of a key extracellular protein, which is also reduced in keloid scar tissue, and that collagen formation is abnormal in fibroids. These observations suggest that fibroid tumors may be caused by altered production of proteins that make up the extracellular matrix. Extramurally, NICHD and ORWH co-fund eight basic science and translational projects that will strengthen the science base, improve understanding of how uterine fibroids develop and grow, and provide clues to more effective conservative management that will go a long way to preserve the fertility and reproductive health of all women. NIEHS supports the *Uterine Fibroid Study* to define the cause of fibroids as 80% of African-American women and nearly 70% of Caucasian women develop them before they reach menopause. NIEHS and NCMHD are conducting an epidemiological-based study to investigate uterine fibroid growth. The study focuses on prevention strategies in high-risk women and the development of new therapies to reduce the need for hysterectomies. NIEHS is evaluating environmental components of this disease through exposure studies, using cell culture systems and animal models. Other NIEHS leiomyoma research focuses on the molecular mechanisms of this disorder in human and animal models as they relate to the role of growth factors, receptor signaling pathways, and cell growth/cell death regulatory proteins in the progression and development of these tumors. In addition to supporting uterine fibroid research, ORWH, with NIEHS, NICHD, other NIH institutes and centers, and DHHS agencies, is sponsoring a February 2005 conference, *Advances in Uterine Leiomyoma Research: Second NIH International Congress*. This scientific conference is bringing together researchers in the fields of biomedicine, epidemiology, basic research, therapeutics, and translational medicine to foster an

exchange of scientific information among members of the uterine leiomyoma research, health care communities, and industry. This collaborative effort will strengthen the trans-NIH research on uterine fibroids.

Item

Office of Rare Disease Research – . . . .The Committee commends the Director of NIH and ORD for the rapid progress over the past eighteen months since the office was created in statute and given additional responsibilities. The Committee appreciates the initiation of the rare disease clinical research network, and encourages research aimed at the development of interventions for orphan diseases, including cystic fibrosis. The Committee also encourages NIH to pursue exploratory grants and proof of concept studies for the development of new therapeutics in the treatment of rare diseases and to intensify support of the training of clinical research investigators in rare diseases. (p. 107)

Action taken or to be taken

Currently, ORD together with the NIH Institutes supports ten Rare Diseases Clinical Research Consortia. The Genetic Diseases of Mucociliary Clearance Consortium includes a focus on variants of cystic fibrosis (also see the Senate item on cystic fibrosis, page 2 of this submission.) The Rare Diseases Clinical Research Network includes attracting and training highly qualified investigators in these rare diseases. Also, in 2004, ORD added support for pilot studies and demonstration projects available to all consortia that can include exploratory grants and proof of concept studies for the development of new therapeutics in the treatment of rare diseases.

In addition, the ORD cosponsors a program announcement with the National Heart, Lung, and Blood Institute (NHLBI) for pilot studies, demonstration projects, and exploratory research studies targeted to develop candidates for therapies. ORD funded an application to screen virulence inhibitors as candidate therapeutics in cystic fibrosis (CF) since there is an urgent need to develop new classes of antimicrobials active against *Pseudomonas aeruginosa* which causes chronic respiratory infection in patients with cystic fibrosis.

Item

Public health relevance of awards – The Committee is encouraged by steps NIH is taking to improve communications regarding the public health relevance of its research awards. Specifically, the Committee is pleased NIH has proposed a modification to its standard grant application, PHS Form 398, requiring all grantees to include a statement of public health significance. The Committee urges the Department and the Office of Management and Budget to approve the proposed revision and support the agency in its efforts to implement this important change in the grant application form. (p. 107)

Action taken or to be taken

The proposed modifications of the standard grant application, PHS Form 398, have received approval from the Department and the Office of Management and Budget. The revisions were published on November 2, 2004 including the instruction for the Principal Investigator to succinctly describe the relevance of the proposed research to public health. See Guide Notice dated 11/2/04 http://grants.nih.gov/grants/guide/notice-files/NOT-OD-05-006.html.

Item

NIH Roadmap and Clinical Practice – The Director of NIH is commended for his Roadmap efforts to re-engineer clinical research as currently supported by NIH. The Committee recognizes that it is essential that study results be rapidly disseminated into clinical practice. The Director is encouraged to work directly with the medical community, including the surgical community, in order to utilize existing networks as a way to accelerate the transfer of information for the treatment of patients. (p. 108)

Action taken or to be taken

The NIH Roadmap for Medical Research is an agency-wide effort in which all institutes and centers work together to develop initiatives that will facilitate discovery, strengthen the research enterprise, and accelerate the development of tomorrow's treatments and cures. The NIH Roadmap initiatives are ones that the NIH as a whole must address. Initiatives within Re-engineering the Clinical Research Enterprise, one of three theme areas of the NIH Roadmap, are focused on improving clinical research through facilitating translational research, developing technologies to measure patient-reported symptoms, adopting a systematic infrastructure and policies that will better serve the evolving field of scientific discovery, and preparing the future clinical research workforce. Ultimately, these efforts will enhance the quality and efficiency of the nation's clinical research enterprise. The involvement of patient communities and community-based health care providers, a concept imbedded in these efforts, is critical to the success of re-engineering the clinical research enterprise.

Re-engineering the clinical research workforce: The promise of 21st century medicine cannot be fulfilled unless we have clinical researchers whose skills match the increasing complexity and multidisciplinary nature of science. The creation of "clinical research teams" that involve community-based practitioners will also be key. NIH Roadmap efforts seek to embrace and train an ever broadening array of scientists and practitioners to meet new challenges in clinical research. In 2004, several national workshops with leaders of the academic medicine community, investigated ways to expand the pipeline of students entering clinical research, train future leaders and create viable career pathways for clinical researchers. The Multidisciplinary Research Career Development Program supports seven institutions in clinical research career development of post-doctoral-level scholars and young faculty members from a variety of scientific and medical disciplines. These scholars will be trained in patient oriented research, translational research, small and large scale clinical investigation and trials, and epidemiologic and natural history studies. A new solicitation focuses on establishing a predoctoral clinical research training program to stimulate the interest of medical, dental, nursing and other allied health students in clinical research careers. To assist the translation of large-scale studies and proven concepts into practice at the community level, the development and feasibility testing of a conceptual model is underway for a National Clinical Research Associates Program (NCRA). The NCRA will include community practitioners (physicians, dentists, and nurse practitioners) as active members of the "community of research." They will participate in clinical research, referring and following their patients in clinical studies, and accelerating the transfer of research findings into their practice and their communities.

Enhanced networking: Building upon the existing strengths of the clinical research enterprise and extending its capacity is the basis for several NIH Roadmap initiatives. These initiatives are exploring the features of current systems in order to identify best practices and to test ways to link existing clinical research networks and augment their interoperability. An inventory of existing clinical research networks is being conducted to identify characteristics that promote or inhibit successful network interactivity and productivity. A conference will convene in 18 months to report the inventory results and highlight best practices. In a parallel effort, a Broad Agency Announcement has issued 12 awards to pilot test approaches for facilitating communication and cooperation among networks, thereby promoting collaborations, increasing access to data and resources, and enhancing opportunities for discovery and development of clinical interventions. The outcome of these two activities will serve to inform the design and development of a National Electronics Clinical Trials and Research (NECTAR) network – with standardized data management techniques and increased sharing of information, samples, and other resources. In addition NIH Roadmap efforts to catalyze the coordination and harmonization of policies germane to the conduct and oversight of clinical research are now underway. Communication and collaborations with other relevant government agencies is a central feature of these efforts, as is consultation with key stakeholders, through briefings of groups representing academic medicine and prominent scientific societies.

Translational Research and Clinical Research Technologies: Key to accelerating the bi-directional bench to bedside translation of biomedical discovery is the increased interaction between basic and clinical scientists and the movement of powerful new tools from the laboratory to the clinic. The NIH is currently soliciting applications for planning grants for conceptualizing and development of Regional Translation Research Centers. Ultimately formal centers will provide critical research resources regionally and nationally to facilitate the research for the development and testing of potential treatments. At the same time, a network composed of seven NIH-funded Roadmap grants aims to improve assessment of patient-reported clinical outcomes. Valid and reliable measurement of symptoms and aspects of health-related quality of life is especially critical in chronic diseases, in which biological indicators are often not closely related to disability, distress, or to benefit derived from treatment. The Patient-Reported Outcomes Measurement Information System (PROMIS) network will develop a publicly available item bank and computerized adaptive testing to enhance measurement of subjective outcomes in clinical research.

Further information about the NIH Roadmap can be found at: http://nihroadmap.nih.gov.

Item

Best pharmaceuticals for children- The Committee recognizes the importance of ensuring that drugs are safe and effective for use by children. The Committee supports continued implementation by NIH of the Best Pharmaceuticals for Children Act of 2002 to support the pediatric testing of off-patent drugs, as well as on-patent drugs not being studied through existing mechanisms. In implementing this responsibility, NICHD should act as coordinator for all other institutes within NIH for which pediatric pharmacological drug research may have therapeutic relevance. NICHD is also encouraged to consult with the Food and Drug Administration to ensure that the studies conducted are designed to yield improved pediatric labeling. The

Committee requests NIH to provide an update during its annual appropriations testimony on the number of studies supported; the estimated cost of each study undertaken; the number of label changes resulting from completed studies; the patent status of the drugs studied; and the number of drugs remaining on the priority list. NICHD should focus its resources on encouraging the study of drugs where there is a medical necessity to conduct clinical pediatric studies, consistent with ethical concerns. The Committee also urges NICHD to give full consideration to existing information that supports the safe use of drugs in children and use of conditions contained in the Pediatric Research Equity Act to identify drugs for study and to determine the scope and magnitude of those studies. (p. 108)

Action taken or to be taken

The NICHD agrees that drugs prescribed for use in children should be safe and effective, and that physicians need to know how best to treat children with these drugs. The NICHD is currently preparing a report on the number of studies supported; the estimated cost of each study undertaken; the number of label changes resulting from completed studies; the patent status of the drugs studied; and the number of drugs remaining on the priority list. This report will be forwarded to the House and Senate Appropriations Committees prior to the NICHD FY 2006 hearings.

To implement the Best Pharmaceuticals for Children Act (BPCA), the NICHD is coordinating its activities closely with other NIH Institutes/Centers and the Food and Drug Administration (FDA). In FY 2004, the NICHD supported a series of Intra-Agency Agreements (IAAs) and other actions under the BPCA. These include:

- An IAA with the National Cancer Institute's (NCI) Children's Oncology Group (COG), to study Vincristine and Dactinomycin for malignancies in children.
- An IAA with FDA to conduct primate studies to evaluate the scientific and safety concerns about the use of Ketamine as an anesthetic in children.
- An IAA with the National Institute of Environmental Health Services (NIEHS) to acquire literature relating to the developmental and reproductive effects, general toxicity, and pharmacokinetics of Lindane.
- A series of meetings and presentations with National Institute of Mental Health (NIMH) for the purposes of locating on-going pediatric clinical trials within NIMH. Additionally, the NICHD is acquiring data sets created under an NIMH study that will enhance information the NICHD seeks to gather from a study of Lithium as it is used to treat bipolar disorder in the pediatric population.
- A contract with the Institute of Medicine (IOM) to identify and evaluate ethical issues concerning clinical trials in pediatric populations.

In January 2004, the NICHD established a working group to collaboratively identify off-patent drugs for listing. In July 2004, the NICHD conducted its annual meeting with other NIH Institutes to discuss the status of FDA's Written Requests (WR) and to seek input regarding the 2005 List Process. The process has evolved so that each year approximately 15 off-patent drugs will be identified as highest priority for testing, from a total of about 180 drugs used in pediatric age groups. The criteria for selecting these drugs include the frequency of use and overall public health impact.

With regard to on-patent drugs, and as of this writing, the FDA has referred five drugs and their specific indications to the Foundation for the NIH (FNIH) to consider for support of needed studies in children. These drugs include: Baclofen for the oral treatment of spasticity, most commonly from cerebral palsy; Bupropion for depression and smoking cessation; Sevelamer for hyperphosphatemia in chronic renal insufficiency; Morphine for pain; and Zonisamide for partial seizures.

To support the safe use of drugs in children and in accordance with the Pediatric Research Equity Act (PREA), the NICHD is supporting the collection of existing information from previous pediatric drug studies. These processes include systematic literature reviews and meta-analysis; collection of data on frequency of use of medication by pediatric age; collection of data on frequency of conditions among pediatric age groups; evaluations of safety/efficacy data by age in pediatric cancer patients; and collaboration with NIMH to utilize data gathered in multi-center trials of drugs in children.

Item

Autism spectrum disorders- The Committee is pleased with NIH's autism research matrix and encourages NIH to devote sufficient resources to this research agenda. When implementing the autism research matrix, the Committee encourages NIH to coordinate with autism organizations already funding research initiatives to ensure the most efficient use of resources. The Committee also notes the promise of particular areas cited in the matrix, including genetic and behavioral characterization of the disorder, screening and early diagnosis. (p. 109)

Action taken or to be taken

The NIH Autism Coordinating Committee is actively working towards achieving the research agenda of the Autism Research Matrix. The April 2004 reissue of the program announcement "Research on Autism and Autism Spectrum Disorders" was designed to support the matrix research goals. NIH support of autism research grew from $22 million in FY 1997 to $93 million in FY 2003.

Coordination with Outside Organizations: As indicated in the request for the Autism Research Matrix, opportunities for collaboration with voluntary and private funding organizations, as well as other governmental agencies, are essential to maximize resources. Five NIH Institutes, three institutes of the Canadian Institutes of Health Research (CIHR), the Health Research Board, Ireland (HRB), the Southwest Autism Research & Resource Center (SARRC), Cure Autism Now (CAN) and the National Alliance for Autism Research (NAAR) are working together to develop a new research initiative ($21.5 million over 5 years) to identify specific genes and gene variants in localized chromosomal regions that produce susceptibility to autism.

NIH Institutes are partnering with NAAR on several other initiatives. The NICHD, NIMH, and NAAR have formed a consortium of researchers focusing on the study of infant siblings of children with autism, to help identify early features and distinguishing characteristics of autism. The National Institute on Deafness and Other Communication Disorders and NAAR co-

sponsored several meetings on language and autism, which resulted in the recent establishment of a fellowship program to enhance research on the interface between autism and language, including linguistic and augmentative communication strategies.

Genetics and Behavioral Characterization: A primary short term autism research matrix goal in the area of genetics and behavioral characterization is to define and plan the comprehensive biomedical and behavioral characterization of autism by delineating core and associated features, onset, longitudinal course, and subtypes of the disease (i.e. phenome), using various research strategies. Other matrix goals in this area include establishing resources for genotype/phenotype studies, studying existing data, developing a twin registry, and developing non-brain biomarkers. Activities underway to achieve these include the establishment of a genetics repository and funding supplements for genetic samples, the funding of a twin study, and planning for an NIH sponsored meeting on state of the science with respect to the autism phenome. In addition, the NIH Autism Coordinating Committee is working with the National Center for Research Resources - Biomedical Informatics Research Network, as well as NIH Center for Information Technology, in order to create a research database intended for long term use by the research community.

Screening and Early Diagnosis: Several initiatives are underway to promote screening and early diagnosis of autism. The Interagency Autism Coordinating Committee (IACC) has established a subcommittee on autism screening, which is actively engaged in facilitating the implementation of screening practices into the community. The CDC is currently partnering with several private organizations to launch the awareness campaign: "Learn the Signs. Act Early, " to encourage early screening and detection of autism and other developmental disabilities.

Item

Autism and Vaccine – The Committee continues to be aware of concerns about reports of a possible association between the measles component of the measles-mumps-rubella (MMR) vaccine and a subset of autism termed autistic entercolitis. The Committee continues its interest in this issue and encourages the Interagency Coordinating Committee to continue to give serious attention to these reports. The Committee is aware that research is underway, supported by NIH, and encourages NIH to avoid delays in this research. The Committee is also concerned that there is some evidence that infant exposures to thimerosal in the 1990s may be related to the epidemic of neurodevelopmental disorders in children. CDC's most extensive review of Vaccine Safety Datalink data concluded that more research needs to be conducted in this arena to answer these questions with certainty and the Committee concurs with the need for this continued research. The Committee encourages NIH to dedicate significant resources to pursue the recommended research initiatives outlined in the Institute of Medicine's (IOM) Immunization Review. These reports have identified the research needed to better understand why a number of children suffer severe adverse reactions to childhood vaccines. Continuation of this research to develop a better understanding of biological mechanisms is critical for knowing with certainty whether or not thimerosal and other vaccines exposures might cause increased risks for some children. (p. 110)

Action taken or to be taken

The (NIH) remains strongly committed to vaccine safety. The evaluation of vaccine safety is an essential component of every vaccine clinical trial that is conducted or sponsored by NIH. All trials include an assessment of vaccine safety as a primary study objective. Study participants are closely monitored for any adverse effects of the vaccinations they receive. In addition to research on new vaccines, NIH devotes substantial resources to developing improved vaccines that are more effective and have fewer side effects than currently licensed vaccine. NIH also pursues research to address specific vaccine safety research hypotheses as they arise, as in the case with thimerosal.

Thimerosal is a preservative added to some vaccines and other pharmaceutical products because it is effective in killing bacteria and in preventing bacterial contamination of the product. When thimerosal is degraded or metabolized, one product is ethyl mercury. In July 1999, U.S. Department of Health and Human Services agencies, the American Academy of Pediatrics, and vaccine manufacturers agreed that thimerosal should be reduced in or eliminated from infant and childhood vaccines as a precautionary measure and to reduce human exposure to mercury from all sources. This decision was based on U.S. and international guidelines for methyl mercury exposure (usually associated with ingestion of certain foods, particularly fish) and the assumption that the health risks from methyl and ethyl mercury are the same.

Additional research is needed to determine whether the guidelines for methyl mercury are also appropriate guidelines for thimerosal. For example, in its May 2004 report "Vaccines and Autism," the Institute of Medicine (IOM) Immunization Safety Review Committee recommended increased research efforts to quantify the level of exposure to thimerosal and other forms of mercury in infants, children, and pregnant women. NIH has initiated several research activities designed to better understand what happens to thimerosal once it is introduced into the body and how this compares to current knowledge of methyl mercury metabolic pathways. For example, the National Institute of Allergy and Infectious Diseases (NIAID) supported initial studies at the University of Rochester and supports follow-up studies in Argentina to measure mercury in the blood and other samples from infants who received routine immunizations with thimerosal-containing vaccines. NIAID and the National Institute of Environmental Health Sciences (NIEHS) have also cosponsored a study in infant macaques to examine the pharmacokinetics and tissue distribution of thimerosal (by injection) and methyl mercury (by oral ingestion) to provide information to address whether the exposure levels established as safe for methyl mercury are also appropriate for exposure limits on ethyl mercury. This study produced data suggesting a faster clearance of mercury from blood and brain with thimerosal than occurs with oral methyl mercury; these data have been submitted for publication. NIEHS has also conducted studies in mice of the tissue distribution of total mercury following an acute intramuscular injection of various forms of mercury, including methyl mercury, ethyl mercury and thimerosal compared to the tissue distribution of total mercury following oral ingestion of methyl mercury. This study demonstrated significant differences in the distribution of mercury depending on the route of administration, with greater absorption following oral administration than with intramuscular injection; these data have been published.

In addition, several projects within the NIEHS-supported Center for Children's Environmental Health and Disease Prevention Research at the University of California, Davis, include work on thimerosal. One such project is the first case-controlled epidemiological study of environmental factors in the etiology of autism. Thimerosal is one of several chemicals being investigated to determine whether exposure may act synergistically with unidentified susceptibility genetic factors to produce autism spectrum disorders. A second project aims to develop animal models to assess social behavior in developing and mature animals; this will allow an examination of the effects of various toxicants, such as thimerosal, on the development and performance of social behaviors. A third project seeks to identify molecular and cellular mechanisms that may underlie responses of autistic children to chemicals to which they are exposed during fetal development and periods of early postnatal brain development. Lastly, a project recently initiated through the support of NIEHS and the National Toxicology Program will examine the effects of thimerosal administration on behavior and brain structure in an autoimmune-prone strain of mice known to be sensitive to mercury. These studies are based on a recent publication showing that mice with genetic differences in immune system competence differed in their response to thimerosal. The new NIEHS-supported studies will incorporate a number of additional important factors including direct measurement of social behavior, rigorous quantification of brain structure, and measurement of distribution of mercury in blood and brain.

Finally, while NIH is not supporting any research to investigate a possible association between the measles-mumps-rubella (MMR) vaccine and a subset of autism termed autistic entercolitis, the U.S. Centers for Disease Control and Prevention is supporting a study to investigate whether the strain of measles virus that is present in the MMR vaccine is present in the intestines of some children with autistic spectrum disorders.

Given the importance of vaccines as a public health tool, NIH will continue to aggressively address vaccine safety concerns as they arise to ensure that the safest and most effective vaccines are available to the public.

Item

Vaccine safety research **--** The Committee is also concerned that there is some evidence that infant exposures to thimerosal in the 1990s may be related to the epidemic of neurodevelopmental disorders in children. CDC's most extensive review of Vaccine Safety Datalink data concluded that more research needs to be conducted in this arena to answer these questions with certainty and the Committee concurs with the need for this continued research. (p. 110)

Action taken or to be taken

Please refer to page OD-39 of this document, ***Autism and vaccine***, for NIH's response to this significant item regarding vaccine safety research.

Item

Vaccine safety research **--**The Committee encourages NIH to dedicate significant resources to pursue the recommended research initiatives outlined in the Institute of Medicine's (IOM) Immunization Review. These reports have identified the research needed to better understand

why a number of children suffer severe adverse reactions to childhood vaccines. Continuation of this research to develop a better understanding of biological mechanisms is critical for knowing with certainty whether or not thimerosal and other vaccines exposures might cause increased risks for some children. (p. 110)

Action taken or to be taken

Please refer to page OD-39, ***Autism and vaccine***, of this document for NIH's response to this significant item regarding vaccine safety research.

Item

Autoimmune diseases – The Committee appreciates the NIH Autoimmune Diseases Coordinating Committee (ADCC) and the comprehensive Autoimmune Diseases Research Plan it prepared. The Autoimmune Diseases Coordinating Committee (with representation from each NIH Institute, Centers for Disease Control and Prevention, Food and Drug Administration, Veterans Administration, and patient advocacy organizations) has been effective in fostering collaborative, integrated multi-Institute research on issues affecting the entire genetically related family of autoimmune diseases. The ADCC's effectiveness in promoting inter-Institute collaboration on high priority cross-cutting research identified in the Autoimmune Diseases Research Plan has been a significant factor in achieving recent advances in the understanding, diagnosis and treatment of the autoimmune family of diseases. The Committee hopes that NIH will target the high-priority cross-cutting research identified in the Autoimmune Diseases Research Plan research. (p. 110)

Action taken or to be taken

The National Institutes of Health (NIH) remain deeply committed to research to improve the diagnosis, prevention, and treatment of autoimmune diseases. In December 2002, NIH transmitted the NIH Autoimmune Diseases Research Plan to Congress, in fulfillment of the requirements for a plan and biennial report under the Children's Health Act of 2000 (P.L. 106-310).

The NIH Autoimmune Diseases Research Plan was prepared by the NIH Autoimmune Diseases Coordinating Committee (ADCC) and reviewed by an expert panel that included scientists, clinicians, and representatives from constituency groups. The ADCC, which was established in 1998, under the direction of the National Institute of Allergy and Infectious Diseases, facilitates collaboration among those NIH Institutes, Offices, and Centers, other Federal agencies, and private organizations with an interest in autoimmune diseases.

The ADCC Research Plan is a comprehensive, long-term agenda for autoimmune diseases research which describes four areas central to progress for all autoimmune diseases and offers recommendations for addressing them. These areas are burden of disease; etiology; treatment, prevention, and diagnosis; and training, education, and information dissemination. The Plan highlights many unprecedented opportunities to increase the understanding of autoimmune diseases, with a conceptual focus on the underlying mechanisms shared by many autoimmune

diseases. Understanding the commonalities of this family of heterogeneous diseases may facilitate the translation of new knowledge into more effective treatment and prevention strategies.

The ADCC will submit its second report to Congress in the spring of 2005. This report will summarize NIH's research activities and accomplishments in autoimmune disease research, including ongoing research projects and future initiatives that address components of the ADCC Autoimmune Diseases Research Plan. This report will identify the related research activities and funding of the many NIH Institutes and Centers who support research on autoimmune diseases, including the National Institute of Allergy and Infectious Diseases, the National Institute of Arthritis and Musculoskeletal and Skin Diseases, the National Institute of Diabetes and Digestive and Kidney Diseases, the National Eye Institute, the National Institute of Neurological Disorders and Stroke, and the National Heart, Lung, and Blood Institute, to name a few.

Item

Research infrastructure at minority health professions institutions – The Committee continues to be pleased with the NIH Director's implementation of various programs focused on developing research infrastructure at minority health professions institutions. The Committee encourages the NIH Director to work closely with the Director of the NCMHD to ensure coordination among these various mechanisms to partner with minority health professions schools to address their infrastructure needs. (p. 111)

Action taken or to be taken

Piloted in FY 2001 and fully implemented in FY 2002 as an ongoing initiative, NCMHD has plans to continue supporting the Research Endowment program in FY 2006. This program is an important priority of the Center and is considered to be an ongoing initiative. The Research Endowment Program generates funds to help build research and training capacity in institutions that make significant investments in the education and training of underrepresented minority and socio-economically disadvantaged individuals. The Research Endowment program seeks to 1) close the disparity gap in the burden of illness and death experienced by racial and ethnic minority Americans; 2) overcome educational and financial resource barriers to promote a diverse and strong scientific, technological and engineering workforce in the 21st century; and 3) increase the participation of underrepresented minorities in the biomedical, scientific, technological and engineering workforce.

Through the NCMHD Centers of Excellence in Partnerships for Community Outreach, Research on Health Disparities and Training (Project EXPORT) the NCMHD funds collaborative research efforts, which enable institutions at all levels of capacity to maximize their health disparities research efforts. Through this program, the NCMHD engages communities in the effort to eradicate health disparities; builds research capacity at minority-serving institutions; promotes participation in biomedical and behavioral research among health disparity populations; and increases participation in health disparities research.

The Research Infrastructure in Minority Institutions (RIMI) Program supports institutions that enroll a significant number of students from minority health disparity populations to develop and

enhance their capacity and their competitiveness to conduct biomedical research. The RIMI Program also assists non-doctoral degree institutions to develop their research infrastructure, primarily through collaborations with research-intensive universities. RIMI Program grants also include an optional one-time allocation for relevant facilities renovations for which applicants may apply.

The NIH Director worked closely with the Director of NCMHD to implement these research infrastructure programs. The NIH Director will continue to work closely with the NCMHD Director to coordinate these efforts to support the research infrastructure at minority health professions schools.

Item

Heart disease, stroke and other cardiovascular diseases- The Committee recognizes that the problems associated with heart disease, stroke and other cardiovascular diseases involve many institutes and centers, including NHLBI, NINDS, NIA, NIDCR, and NCRR. The Committee urges the Director of NIH to intensify his coordination of cross-cutting research on these diseases in all institutes and centers as appropriate and requests that the Director be prepared to report to the Committee on these initiatives in the FY2006 budget hearings. (p. 111)

Action taken or to be taken

The NIH supports an extensive array of initiatives on heart disease, stroke, and other cardiovascular diseases**.** Additional activities are scheduled to begin in 2005. The NIH Director will be prepared to report on initiatives on these diseases begun in fiscal year 2004 or scheduled to begin in fiscal year 2005 at the fiscal year 2006 appropriations hearings.

Item

Vascular biology – The Committee recognizes the importance of advancing research in the field of vascular biology, the study of blood and blood vessels and their interactions. Not only is the maintenance of the blood supply critical to the functioning of all organs of the body, understanding the mechanisms and treatment of diseases that interrupt the blood supply is relevant to all organ systems and their disorders. Research into vascular biology can provide the scientific basis for new therapies to prevent thrombosis, therapies that are important to the prevention and control of heart disease, stroke, recurrent fetal loss, and complications associated with sickle cell anemia and diabetes, and therapies related to the interruption of the blood supply to tumors and cancers. The Committee encourages the NIH director, working with the individual institutes and relevant voluntary health organizations, to develop a comprehensive NIH-wide approach to identify and pursue research opportunities in this field. (p. 111)

Action taken or to be taken

The NIH has a strong commitment to programs that enhance both basic and clinical research in vascular biology. In an effort to develop a comprehensive NIH-wide approach to identify and pursue research opportunities in this field, in 2004 the National Heart, Lung, and Blood Institute (NHLBI), the National Cancer Institute (NCI), the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Eye Institute (NEI), the National Institute of Neurological Disorders and Stroke (NINDS), and the Juvenile Diabetes Research Foundation

(JDRF) jointly sponsored a workshop on angiogenesis (development of new blood vessels from preexisting vessels). Based on the recommendations of this workshop, NIH scientific staff formed a Trans-Institute Angiogenesis Research Program (TARP), which has already implemented its first research initiative, "Collaborative Studies on Angiogenesis and Diabetic Complications," cosponsored by the NHLBI, the NIDDK, the NINDS, and the NEI. These institutes, with the NCI and the JDRF, are also establishing a Web site to provide basic and clinical research investigators with information about resources for angiogenesis research and programs at the NIH.

In addition to TARP, a trans-NIH Stroke Working Group was launched in 2004 to foster collaborations among Institutes for stroke-related activities, including development of research initiatives, national meetings, an NIH stroke Web site, and enhanced communications with national stroke associations. As one product of these enhanced collaborations, the NHLBI and the NINDS will jointly implement two new research programs in 2005: "Novel Targets and Therapy Development for Ischemic Stroke" (led by NHLBI) and "Genetics and Pathobiology of Vascular Cognitive Impairment" (led by NINDS, and including National Institute on Aging). The NCI is planning a comprehensive conference around angiogenesis and vascular biology scheduled for early 2005.

Item

Parkinson's Disease – The Committee is interested in the development of NIH's Parkinson's disease `matrix.' The Committee encourages NIH to extend the matrix to include concrete steps toward better treatments and a cure. Since five years have elapsed since the last NIH conference on Parkinson's disease, the Committee encourages the Director to hold another conference, similar to the one held in November of 1999, to examine the path to a cure, working with patient advocacy, scientific, and non-profit communities. The results of the conference should produce a strategic plan setting forth the programs required to secure the earliest possible development of effective therapies, prevention, and a cure for Parkinson's disease. (p. 111)

Action taken or to be taken

The NIH has supported many new Parkinson's disease (PD) research programs and accomplishments over the past five years; however, it also recognizes that the needs of the research community have continued to evolve over this time period. In order to evaluate these needs, and to assess emerging roadblocks to research progress, NIH held a Parkinson's Disease Coordination Summit in July 2002. Following this Summit, the NIH developed the specific recommendations from its participants into a Matrix of short-to-long range, and low-to-high risk goals. While not a guaranteed roadmap to a cure for PD, these goals presented the best opportunities for NIH and the Parkinson's disease voluntary community to help investigators overcome critical roadblocks to research. Since the five-year PD Research Agenda is drawing to a close, and two years have elapsed since the development of the original Matrix, NIH is committed to supporting another Parkinson's Disease Summit meeting, to be held in the summer of 2005, which will involve PD scientists and clinicians, as well as members of the PD voluntary community. At this meeting, NIH will ask the scientific representatives to identify needs and emerging areas of research, to make recommendations regarding remaining roadblocks to

research, and importantly, to prioritize these recommendations. NIH will use these priorities to expand and revise the goals in the PD matrix, as part of an updated strategic plan for managing future NIH research programs on PD.

Item

Lupus - Lupus is a disabling and life-threatening autoimmune disease which affects more than 1.5 million Americans, 90 percent of whom are women. It causes the immune system to attack the body's own cells and organs, including the kidneys, heart, lungs, brain, blood and skin. Lupus is two to three times more common among African Americans, Native Americans, Hispanics, and Asians, than among Caucasians. Lupus is a disease of rampant, uncontrolled inflammation caused by multiple genes. Scientists know some of the specific proteins that trigger lupus and are approaching a time when new strategies in molecular medicine can be applied to improve the function of these proteins and prevent lupus flares. Because lupus is a multifaceted disease, the Committee encourages the Director to ensure that all relevant institutes work closely and collaboratively to maximize the output of our national investment in lupus research. To ensure that progress is maximized, the Committee requests NIH to develop a five-year trans-NIH research plan for the full spectrum of lupus research. Among the institutes to be involved should be NIAMS, NHLBI, NIDDK, NINDS, NIAID, NIEHS, and NCMHD. (p. 111)

Action taken or to be taken

The NIH has taken a leadership role in coordinating Federal research efforts for systemic lupus erythematosus (lupus) through the Lupus Federal Working Group. Established in 2003, the working group provides for the exchange of information and coordinates Federal efforts in lupus research and education. It is comprised of representatives from all relevant HHS agencies and other Federal departments having an interest in lupus. The third meeting of the working group is scheduled for December 2004. Discussions at this meeting will facilitate the development of a 5-year trans-NIH research plan.

Additionally, the NIH supports the NIH Autoimmune Diseases Coordinating Committee (ADCC). The ADCC, which was established in 1998, facilitates collaboration among the NIH Institutes, Offices, and Centers, other Federal agencies, and private organizations with an interest in autoimmune diseases, including lupus. The committee has developed the NIH Autoimmune Diseases Research Plan, a comprehensive, long-range agenda for autoimmune disease research, which describes areas central to progress for all autoimmune diseases and offers recommendations for addressing them. The report identifies many NIH Institutes and Centers who support research on autoimmune diseases including NIAID, NIAMS, NHLBI, NIDDK, NINDS, NEI, and the Office of Research on Women's Health to name just a few.

Item

Spina bifida – The Committee recognizes that spina bifida is the leading permanently disabling birth defect in the U.S. and encourages NIH to put a higher priority on research into primary and secondary prevention of this condition. While through research we have learned that Spina Bifida is highly preventable through proper nutrition, including appropriate folic acid consumption, too many pregnancies are still affected each year by this devastating birth defect. The Committee also acknowledges that prevention does not assist the more than 70,000

individuals living with spina bifida and therefore urges NIH, particularly through NINDS and NICHD, to focus research into secondary prevention for spina bifida. (p.112)

Action taken or to be taken

The NIH is committed to research efforts in the prevention and treatment of spina bifida and associated secondary conditions. The NICHD and the NINDS are the lead Institutes for funding in this area. The NICHD is currently funding a multicenter network trial, the Management of Myelomeningocele study (MOMs) evaluating the safety and efficacy of fetal surgical repair and traditional postnatal repair of open neural tube defects. The three clinical sites are the University of California-San Francisco, Children's Hospital of Philadelphia, and Vanderbilt University and the independent data coordinating center is the George Washington Biostatistical Center. No other US site is offering this procedure outside of the NICHD trial. This study enrolls women in the mid-portion of their pregnancy ,who are carrying infants with diagnosed isolated spina bifida, with a rigorous and common protocol at the three sites. After consenting, they are randomized to receive either prenatal surgery on the mother and fetus or to return at the end of pregnancy to undergo standard closure by the same surgical teams. Follow up will occur over at 3-year period of all 200 patients enrolled in the study. Study endpoints will include an evaluation of the effect on the mother's health during the current pregnancy and in future pregnancies; fetal outcome; and neonatal and infant need for shunting, treatment for orthopedic and urologic problems common to people with spina bifida; and an evaluation of early childhood neurologic and mental functioning. Information about the trial can be found at the website: www.spinabifidamoms.com. Recruitment began in March 2003, of the 200 patients required for the trial, 58 have been randomized as of October 26, 2004.

The NICHD also held a workshop on August 16-17, 2004, entitled "Fetal Treatment: Needs Assessment and Future Directions" to develop a plan for the surgical, maternal-fetal, and neonatal evaluation and treatment of pregnancies which might benefit from *in utero* therapy and for the dissemination of innovations in maternal-fetal surgery.

In addition to the important study described above evaluating the safety and efficacy of prenatal surgical interventions to repair spina bifida, the NICHD, through its Birth Defects Initiative, fosters interactions between basic scientists, clinicians and genetic epidemiologists to identify the genetic and environmental factors associated with genetic susceptibility, ethnic disparities and variability of human malformations as well as to elucidate the developmental processes that go awry leading to the formation of neural tubal defects (NTDs)**.** As part of this program, a project is underway to link nutritional factors, folate status and genetic information from a large number of effected families to define putative risk factors for spina bifida. An important aspect of this project is to assess the relative contributions of both maternally and embryonically expressed genes to the risk of spina bifida. This study has shown that the maternal genotype for several genes involved in folate metabolism is related to the risk of spina bifida in offspring. In addition, the expression of unrelated genes in the embryo is also significantly related to the risk of this birth defect. The involvement of maternal and embryonic genes as well as the influence of the environment underscores the complexity associated with the occurrence of spinal bifida. Information from this and similar studies can be used to inform basic studies using experimentally manipulable model systems that are essential to clarify the underlying

mechanisms of development and to define gene function. Understanding the developmental mechanisms and gene-environmental interactions may help us to develop preventive strategies for those cases of spina bifida that are not preventable by folate supplementation of the diet. In addition, the NICHD recently issued a new Program Announcement (PA) in collaboration with eight other NIH Institutes and AHRQ, entitled "Research Partnerships to Improve Functional Outcomes." This PA seeks specifically to encourage research towards secondary prevention in individuals with disabilities including those with Spina bifida.

The NINDS funds a wide range of research projects relevant to spina bifida, many of which address recommendations of the joint sponsored May 2003 conference, Evidence-Based Practice in Spina Bifida: Developing a Research Agenda, held in Washington, DC. For example, NINDS-supported researchers are studying the causes and the cognitive effects of hydrocephalus, a build up of fluid in the brain that is common in spina bifida patients. The assessment and treatment of hydrocephalus emerged as a priority from the conference. NINDS also funds research aimed at understanding the neural bases of a variety of cognitive processes.

Basic research on the formation of the nervous system may help scientists to decipher the mechanisms underlying the development of spina bifida, and to devise strategies for preventing or treating the disorder. The NINDS funds grants to understand the genetic and environmental causes of spina bifida and to develop prevention and treatment strategies for the disease. Researchers are testing the hypothesis that certain genetic factors may diminish the availability of folate to the fetus, thereby contributing to spina bifida. The ultimate goal of this research is to understand how folate supplements prevent spina bifida, so that folate supplements for pregnant women can be made more effective. NINDS supports a broad portfolio of research on understanding and treating spinal cord damage, whether due to spina bifida or other causes. Projects funded by NINDS include the development of pharmacological, electrical stimulation, and exercise interventions to improve locomotor and arm function, as well as the use of bioengineering strategies to restore function.

The NINDS helped support The Third International Conference on Neural Tube Defects (NTDs), held in September 2003, which brought together researchers from various disciplines to discuss recent advances in basic and clinical research on neural tube defects, which include spina bifida. The principal investigator and organizer of the NTD conference, together with program staff, have organized banking of blood/DNA samples in an NIH repository, allowing sharing of these rare and important biological patient samples. In fall 2005, NINDS, along with ORD, NICHD and NIA, will sponsor a workshop entitled "Hydrocephalus: Myths, New Facts, Clear Directions" to build on collaborations developed at the NTD conference. This workshop will bring together researchers studying mechanisms of hydrocephalus, risk factors and related disorders and will identify research priorities for hydrocephalus.

Item

Tuberous Sclerosis Complex—The Committee is aware that NIH released a strategic plan for tuberous sclerosis complex (TSC) last summer. The Committee encourages NIH to expand the scope of this effort to broaden the research to multiple institutes beyond NINDS and to emphasize research efforts that are specific to TSC. (p. 112)

Action taken or to be taken

The (NIH) strategic plan for tuberous sclerosis (TSC) research was developed with input from the National Institute of Neurological Disorders and Stroke (NINDS), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Institute of Child Health and Human Development (NICHD), National Heart, Lung, and Blood Institute (NHBLI), National Institute of Mental Health (NIMH), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), and National Cancer Institute (NCI), and the majority of these Institutes fund TSC research. NINDS supports studies of the relationship between TSC mutations and the development of neurological abnormalities, elucidation of the molecular pathway through which the TSC genes control cell growth and proliferation, and the development of therapeutic strategies using animal models. NHLBI funds studies on lymphangioleiomyomatosis (LAM), a rare lung disease associated with mutations in TSC genes that occurs sporadically in women and also in women with TSC. Current NHLBI projects are investigating the molecular pathways that lead from mutations in one TSC gene (TSC2) to the abnormal proliferation of smooth muscle cells associated with LAM. NIDDK supports studies on the kidney lesions associated with TSC, including a project to study mechanisms of genetic instability in the region of the TSC2 gene, which leads to disease onset, and a study of the potential role of interferon-gamma in both the pathology and treatment of TSC renal disease. The NCI supports studies on the regulation of TSC1 and TSC2 and how these genes control cell growth, as well as a phase I trial to determine if rapamycin reduces the volume of kidney tumors in TSC patients and a project to develop a genetic test for TSC. The NCI also maintains the TSC1 mutant mouse line and makes the mice available, without charge, to the research community. The NINDS recently established a coordinating committee of program staff representatives from NIDDK, NHLBI, NIAMS, NCI, NIMH, NICHD, and the NIH Office of Rare Diseases to facilitate coordination of the Institutes' TSC portfolios and develop future initiatives focused on TSC, such as workshops or grant solicitations.

Item

Rett syndrome- Rett syndrome is a genetically inherited neurological disorder seen almost exclusively in females and found in many racial and ethnic groups worldwide. It is believed that Rett syndrome affects approximately one in ten thousand live births per year, although recent discoveries about the underlying genetic cause of this disorder may reveal significantly more affected people than previously diagnosed. The Committee is very encouraged by the most recent advances that have taken place in Rett syndrome research. Important breakthroughs in methods to detect previously undetected genetic variations and, most importantly, critical new discoveries in understanding the genetics of Rett syndrome are likely to catapult treatments not only for Rett syndrome but pave the way for greater understanding of other neurological impairments ranging from autism to schizophrenia. The Committee applauds the excellent program area developed by the NIH and encourages NIH to continue to target its research efforts to ascertain how the genes involved in Rett syndrome and the associated proteins affect other genes and tissues during the development of the nervous system. Furthermore, NIH is encouraged to support the development of animal models, as well as genotype and phenotype investigations of Rett syndrome that could hasten progress in eliminating this and other neurologically based disorders The Committee notes there is also need for expanded research on

the daily problems that affect children with Rett syndrome, including autonomic disorders, such as respiratory, gastrointestinal, circulatory and cardiac disorders, seizures, and scoliosis. Additionally, the Committee recognizes that research in applied areas such as interventions and technological aids for improved literacy and communication will improve the quality of life for Rett syndrome patients and those with other communicative disorders. Since Rett syndrome is a multi-faceted disorder, the Committee encourages NIH to partner with existing advocacy groups and to continue to work to promote continuity across Institutes in their Rett syndrome research. (p. 112)

Action taken or to be taken

The NIH continues to support research in Rett syndrome involving critical new discoveries in the understanding of Rett syndrome genetics that may lead to treatments not only for Rett syndrome, but other neurological impairments ranging from autism to schizophrenia. The NICHD has collaborated with the Office of Rare Diseases in establishing Rare Disease Research Centers, one of which has a focus on Rett syndrome. These include grants aimed also at daily problems that affect children with Rett syndrome.

Recently, the NICHD and NINDS began planning a Memorandum of Understanding with the Rett Syndrome Research Foundation and International Rett Syndrome Association concerning the reissue of a program announcement on Rett syndrome. It is anticipated that the NICHD will contribute to this new effort.

Item

Cystic fibrosis – The NIH Roadmap identifies the re-engineering of the clinical research system as a top priority. One of the strategies that the Roadmap recommends to enhance clinical research is establishing clinical trials networks that share informatics and other technologies. These networks are envisioned to include a significant number of institutions, in order to facilitate efficient recruitment and rapid enrollment of trial participants. An existing clinical trials network for testing therapies for cystic fibrosis (CF) includes many of the elements that have been cited in the Roadmap as critical for any model clinical trials system. The CF system includes: (1) centralized data management and analysis capability, (2) centralized data safety monitoring, and (3) the participation of eighteen institutions, which ensures rapid accrual to trials. The Committee believes that there are important opportunities for collaboration between NIH and this clinical trials network and encourages NIH to pursue this potential collaboration. One benefit of this collaboration would be the ability for NIH to evaluate the impact and benefits of this clinical trials network, its cost efficiencies, and the application of its core features to other diseases and in other settings. (p. 113)

Action taken or to be taken

Two institutes of the NIH, NIDDK and NHLBI, have major research programs aimed at combating cystic fibrosis. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funds both basic and clinical research in cystic fibrosis (CF), maintaining a large portfolio of grants to study and improve treatment of the disease. The Institute recognizes the potential value of the Therapeutics Development Network (TDN), a unique resource for the CF research community, funded by the Cystic Fibrosis Foundation (CFF) and the NIH National

Center for Research Resources. The NIDDK is taking advantage of the opportunities the network affords in funding *Inhaled Tobramycin in Young Cystic Fibrosis Patients*, a randomized controlled trial which is being conducted in the several clinical centers of the TDN. The study seeks to assess the safety and efficacy of an inhaled antibiotic for treating one of the most common and devastating complications of cystic fibrosis, infection by *Pseudomonas aeruginosa*.

Similarly, a major commitment of the National Heart, Lung, and Blood Institute (NHLBI) is to supporting clinical trials and clinical trial networks for the management of respiratory diseases, including CF. In FY2004, the NHLBI, in an enabling partnership with the NIDDK, the CFF, and several companies, is sponsoring an investigator-initiated multi-center clinical trial, *Early Antipseudomonal Therapy in Cystic Fibrosis.* This is the largest clinical trial involving young (1 to 12 year old) children with CF ever to be conducted in the United States, and would be impractical without the TDN infrastructure. The trial seeks to determine the best treatment for initial *Pseudomonas* infection to delay or prevent chronic infections that lead to irreversible lung destruction and eventual death.

The NIH Office of Rare Diseases (ORD) works very closely with NIH Institutes and Centers and Offices, including the NIDDK and NHLBI. Within the area of cystic fibrosis, ORD is cofunding with other NIH Institutes and Centers the Consortium of Genetic Disorders of Mucocilliary Clearance Consortium. The consortium members will collaborate in diagnostic, genetic, and other studies in patients with genetic impairments in mucociliary clearance including variant forms of CF. Patients with these unusual disorders with increased morbidity and mortality often have delayed (or incorrect) diagnoses, because diagnostic tests are not readily available. The consortium utilizes a geographically disbursed, broad-based systematic approach to the diagnostic evaluation of patients that will yield more precise diagnostic criteria and better diagnostic techniques. This collaborative effort will improve care in a number of ways including defining clinical practice guidelines. In addition, pilot projects are designed to develop better diagnostic tools, biomarkers, and screening tests to characterize the respiratory pathobiology, and evaluate novel therapeutic agents. The existing training program in rare airway diseases will be extended to established and young investigators. Trial participants can register at the four geographically dispersed sites or through a web-based registry.

Item

Lymphatic system research – Despite the central role of the lymphatic system in human health and disease, this focus of research and medical care has, until recently, been relatively neglected. The Committee believes that scientists and clinical educators should be alerted to the scientific opportunities and resources that exist to undertake basic and clinical investigation into the role of the lymphatic system in human health and disease. Therefore, the Committee encourages the Trans-NIH coordinating Committee for the Lymphatic System, in collaboration with the OD Office of Communications and relevant institute offices of communications, to implement a comprehensive lymphatic research awareness campaign to inform academia, governmental agencies, industry and scientific and medical professional organizations and to create a heightened comprehension of the central role occupied by the lymphatic system in the maintenance of human health. (p. 113)

Actions taken or to be taken:
The Trans-NIH Coordinating Committee for the Lymphatic System continues to facilitate and implement initiatives and programs in lymphatic research, and has established a subcommittee of communications officers from most NIH components to collaborate on promoting awareness of lymphatic diseases. Initiatives for developing reagents, animal models, and functional imaging have been addressed, in part, in a number of NIH Roadmap initiatives that include the lymphatic vessels. The newly created Trans-NIH Angiogenesis Research Program recognizes the need to establish specialized core facilities for the unique reagents and animal models used in angiogenesis research; these cores would also include reagents and animal models specific to lymphangiogenesis. In addition, the NHLBI will initiate a new program, "Research Career Development Programs in Vascular Medicine," encompassing research on the lymphatic vasculature.

Item
Lymphangioleiomyomatosis (LAM) – The Committee remains very interested in efforts to find a cure for LAM, a progressive and often fatal lung disease of women with no effective treatment. The Committee understands that very recent scientific findings have presented new treatment approaches for clinical testing, and that experimental trials with the drug sirolimus have begun. The Committee encourages NCI, ORD, NINDS and NHLBI to explore opportunities for funding clinical treatment trials through both intramural and extramural means and to use all available mechanisms as appropriate, including support of state-of-the-science symposia and facilitating access to human tissues, to stimulate a broad range of clinical and basic LAM research. The Committee also commends NCRR and ORD for their roles in supporting the Rare Lung Disease Consortium. (p. 114)

Action taken or to be taken
The Office of Rare Diseases (ORD) works very closely with NIH Institutes and Centers. Within the area of rare lung diseases, ORD together with NIH Institutes and Centers supports the Rare Lung Diseases Consortium as part of the Rare Diseases Clinical Research Network. Disorders chosen for the focus of this network include lymphangioleiomyomatosis (LAM). The consortium will facilitate clinical research by promoting collaboration among clinical research centers already focused on research on rare lung diseases, attracting and training highly qualified investigators, collecting clinical data from geographically distributed patients into a large, centralized database, and making the accumulated clinical data available to those affected or possibly affected by a rare lung disease, their clinicians, clinical and basic investigators, and the general public. The consortium includes eleven sites and patient support organization including the LAM Foundation. The consortium will work extensively with the LAM Foundation and other patient support organizations that will provide education for patients, the lay public, and the medical community. Earlier clinical, basic, and translational studies at the centers have already reported critical insights into molecular mechanisms underlying lung function in health and disease.

ORD also provided support for the "The Lymphangioleiomyomatosis (LAM) Foundation International Research Conference" in March 2004. The objectives of this conference were to advance LAM research, to improve LAM clinical practices, and to provide support and inspiration to patients, physicians, and investigators.

ORD will continue to work with the NIH Institutes and the LAM Foundation to explore research opportunities through both intramural and extramural means for support of state-of-the-science symposia and facilitate access to human tissues through the Rare Lung Diseases Registry to stimulate a broad range of clinical and basic LAM research.

Item

Hyperbaric Oxygen Therapy – HBOT is currently in widespread use in medical practice. NIH is encouraged to support meritorious research in this area, especially in basic science, in order to gather evidence regarding the efficacy of HBOT. In particular, studies should consider HBOT as a treatment for various manifestations of reperfusion injury, hemorrhagic shock, trauma injury, surgery patients, stroke and dementia. When appropriate, clinical studies to test the safety and efficacy of this treatment for a variety of conditions should include adult and pediatric populations. NIH is also encouraged to work with professional organizations interested in HBOT as this research moves forward. (p. 114)

Action taken or to be taken

A number of NIH Institutes and Centers continue to fund basic and clinical research on hyperbaric oxygen therapy, including studies of the use of HBOT in treating brain damage resulting from trauma, stroke, and exposure of brain and other organs to radiation during radiotherapy; and wound repair. In addition to these projects, NIH has funded two new grants in FY2004, which are exploring the use of HBOT for treating atherosclerotic lesions and as an adjunctive therapy for sepsis. The NIH continues to be interested in supporting meritorious pre-clinical and clinical studies of HBOT, as appropriate for each specific indication, and welcomes applications in any promising area of research. In 2004, NIH staff continued to meet with staff of professional organizations, as well as with prospective applicants and others interested in HBOT, to encourage well-designed research in this area.

Item

Sepsis—The Committee is aware that sepsis, an overwhelming systemic response to infection that leads to organ dysfunction and death, kills more than 215,000 Americans every year, with direct annual medical costs estimated to exceed $17 billion. Septicemia, a form of sepsis that infects the blood, has been identified by the Centers for Disease Control as the tenth leading cause of death in the United States; sepsis resulting from pneumonia and chemotherapy causes tens of thousands of additional deaths annually. Until recently, therapies proved ineffective. New treatments have been developed which significantly improve prognosis when sepsis is diagnosed in a timely fashion, and new guidelines have been developed to aid health care professionals in identifying the syndrome. Sepsis remains a leading cause of death, however, because too few medical personnel know how to identify and diagnose it. To improve recognition of sepsis among health care providers, the Committee encourages the Office of the Director to work with a national alliance that is focused on sepsis education to create and

implement a program to train infectious disease physicians, emergency room doctors, critical care nurses, and oncologists, especially those in rural and traditionally underserved areas, in the use of the new guidelines to identify sepsis and improve patient outcomes. In particular, the Committee requests the support of NIAID, NHLBI and NCI in these provider education efforts. (p. 115)

Action taken or to be taken

NIH recognizes the growing importance of sepsis and the difficulties in managing this complex disease process. Sepsis, triggered by blood stream infection, is a clinical outcome with a broad spectrum of disease symptoms that range from fever and chills, to severe infections in various organs, to life threatening invasive illnesses. The incidence of sepsis is increasing largely due to 1) advanced medical and technological devices, which can transmit bacteria; 2) the increasing number of immunosuppressed individuals such as the elderly, premature infants, transplant patients, and patients with diseases like HIV or cancer; and 3) the widespread use of antibiotics, which encourages the growth of drug-resistant organisms.

NIH is concerned about sepsis and has undertaken a variety of initiatives to address this issue. For example, the National Institute of Allergy and Infectious Diseases (NIAID) supports a wide array of more than 100 grants related to sepsis, including microbiological and immunological research. In addition, NIAID programs support research on controlling and preventing the spread of bacterial infections, including basic research as well as research on development of diagnostics and interventions.

Rapid and accurate diagnosis is the critical first step in identifying and treating sepsis. Therefore, a new NIAID research initiative, "Sepsis and CAP: Partnerships for Diagnostics Development" was released in August 2004. The purpose of the initiative is to support industry development of broad diagnostic technologies that provide early detection of select major causes of septicemia, bacteremia, candidemia, and community-acquired pneumonia. Five to seven awards are expected to be made in response to this initiative during summer 2005.

By sponsoring and co-sponsoring, with organizations like the National Foundation for Infectious Diseases and the Infectious Diseases Society of America, meetings such as the 2004 Annual Conference on Antimicrobial Resistance, NIAID provides, and will continue to provide, information to the public and to healthcare providers on bacterial infections and antibiotic resistance. In addition, NIAID provides information through its website (www.niaid.nih.gov).

During FY 2005, collaborations between NIH and industry will continue for the development of novel products to address resistant bacterial infections in health-care settings. In particular, NIH will continue to support research on sepsis and related conditions, and to increase public and healthcare provider awareness about this growing medical problem.

Item

Ataxia Telangiectasia (A-T) —A-T is a rare, fatal disease that affects children, causing progressive loss of muscle control, immune system problems, and as high rate of cancer. Recent advances show that A-T research is important not just for patients with A-T, but also for more

prevalent diseases including cancer and neurodegenerative diseases such as Alzheimer's and Parkinson's. The Committee supports the development of an inter-institute coordinating commitee for research on A-T comprised of representatives from all the institutes relevant to A-T, including but not limited to NINDS, NICHD, NCI, NHGRI, NEI, NIA, and NHLBI. The Committee encourages the inter-institute coordinating committee on A-T to conduct workshops with members of the scientific and medical communities to identify important, unanswered scientific questions about A-T and to develop and regularly revise an inter-institute NIH research plan for A-T. (p. 115)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS), National Cancer Institute (NCI), National Heart, Lung, and Blood Institute (NHLBI), and National Institute of General Medical Sciences (NIGMS) currently support research on ataxia telangiectasia (A-T). The program directors from these Institutes have worked together in the past in organizing scientific workshops focused on A-T and have coordinated their A-T portfolios through regular discussions. For example, NINDS and the NIH Office of Rare Diseases (ORD) recently co-sponsored a workshop on drug screening for A-T. Representatives from NCI and NHGRI participated in this workshop and provided expertise based on their experiences with cancer screening programs and the NIH Roadmap Molecular Libraries initiative. To encourage the coordination of future efforts on A-T, the NIH will establish a working group comprised of program directors from all of the Institutes with an interest in A-T. One of the first activities of this working group will be to develop a strategic plan for A-T research, with the input of members of the scientific and medical communities. The members of the working group will meet regularly to assess their A-T grant portfolios, identify gaps, and develop workshops and other initiatives as appropriate to address these gaps.

Item

Sex-based biology – The Institute of Medicine has released a study demonstrating that all biological research must be cognizant of the differences that result from the sex of the patient, tissue or cell. One of the areas where such differences are most pronounced is in the field of neuroscience. For this reason, the Committee encourages the institutes involved in brain research to include sex-based biology as a part of the research conducted and to analyze and report research results in this manner, when appropriate. The Committee would like a report from the Director on the progress of this effort in next year's hearings. (p. 115)

Action taken or to be taken

A significant amount of work related to sex and gender differences is supported by the NIH Office for Women's Health (ORWH) and by the many NIH Institutes and Centers that fund neuroscience research. In fact, the report released by the Institute of Medicine in April 2001 entitled "Exploring the Biological Contributions to Human Health: Does Sex Matter?" was supported in part by the NIH ORWH and several NIH neuroscience Institutes. In addition to the program activities of individual Institutes, the ORWH Agenda for Research on Women's Health for the 21st Century and a number of trans-NIH extramural committees provide opportunities to coordinate NIH efforts to understand sex/gender influences on human neurobiology.

NIH currently supports research to understand the impact of sex and gender differences on human behavior, cognition, perception and disease. For example, several of the Institutes in the NIH Pain Consortium issued a Program Announcement in July 2003 for "Biobehavioral Pain Research" to encourage research on biological contributions to the pain experience. One of the grants funded through this ongoing solicitation focuses on understanding the neural mechanisms of pelvic pain in females. Other recent NIH-supported advances in analgesia research have identified signaling pathways that appear to be major contributors to the sex differences observed in the effectiveness of several pain-relieving agents.

A better understanding of the sex-related factors that influence the symptoms of neurological diseases like multiple sclerosis (MS) is also emerging. Pregnancy often leads to an improvement in the symptoms of MS, and recent NIH-sponsored work in an MS animal model suggests that disease severity in both males and females might be reduced by treatment with estrogen-like compounds. NIH-sponsored investigators are also working to understand the biological pathways through which changes in reproductive hormones (such as those occurring during the menstrual cycle, pregnancy, and menopause) can alter symptoms and/or outcomes in other disorders, such as epilepsy, stroke, and traumatic injury to the nervous system.

Gender-specific analysis of clinical trial results can help to detect differences in male and female risk factors and responses to therapy; since 1993, NIH Grants Policy Guidelines have required that Phase III trials include sufficient numbers of women to carry out valid analyses of gender differences. An example in the area of stroke treatment is the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) – which is directly comparing the efficacy of carotid endarterectomy to angioplasty/stenting, a newer less invasive surgical method – in which investigators have planned analyses of gender differences in the efficacy of the two procedures.

FY 2005 Senate Appropriations Committee Report Language (S. Rpt. 108-345)

Item

Consulting Fees – The Committee was extremely disappointed to learn the extent to which NIH scientists and administrators have been receiving monetary compensation from pharmaceutical and biotechnology companies. Some NIH employees have received hundreds of thousands of dollars for their outside work, none of which was publicly disclosed. Even more disturbing, some of these employees did not disclose their outside work to agency officials. These arrangements raise questions about potential conflicts of interest, the influence that these monetary compensations could have on the outcome of scientific research, and whether these employees are more interested in procuring lucrative consulting fees than in meeting the responsibilities of their full-time, taxpayer-funded jobs. The Committee finds it difficult to understand how the most prestigious biomedical research institution in the world could allow these questions to be raised. The Committee commends the NIH Director for convening a Blue Ribbon Panel to review and make recommendations regarding existing laws, regulations, policies and procedures governing consulting fees. The Committee was also pleased to learn that the NIH plans to implement new regulations to ensure the integrity of its scientific research. While the Committee strongly supports intramural and extramural research at the NIH, it must be sure of the integrity of that research; therefore, the Committee directs the NIH Director to

immediately put in place safeguards that will insure that no conflicts of interest exist between scientists and pharmaceutical and biotechnology companies, or any other entity. (p. 96)

Action taken or to be taken

The NIH was deeply disturbed to learn that some employees may have engaged in outside activities without the requisite prior approval, and that some employees may not have reported the income earned from these activities on their annual financial disclosure reports. Such violations will not be tolerated.

The NIH Director ordered a detailed review of the allegations. The reviews are extensive and should be completed in the near future. The NIH will take appropriate management action against those found to have violated the rules, including, if necessary, making referrals of cases to the DHHS Office of the Inspector General.

Maintaining the public's trust in the integrity of NIH programs and operations is of the utmost concern to NIH. Reviews have led NIH to the conclusion that the current system of oversight is inadequate to assure the public's trust. The NIH Director, with DHHS, took quick and decisive action to rectify these shortcomings. Among the actions taken with, in many cases, the Departments Designated Agency Ethics Official, are the following:

1. Creating the NIH Ethics Advisory Committee, which is comprised of senior NIH scientific staff, to conduct a rigorous peer review of all outside activity requests from high level NIH employees and all requests to consult with pharmaceutical and biotechnology companies.

2. Appointing the NIH Deputy Director as the NIH Deputy Ethics Counselor, and expanding his authority to cover all the top officials in the NIH's Institutes and Centers, so that the ethics function would be consistently administered across the agency for those employees with the broadest programmatic responsibilities.

3. Establishing a Blue Ribbon Panel of renowned experts to delve into the various aspects of the NIH Ethics Program, and propose changes to the program to help restore the public's trust.

4. Requesting and receiving two different equal classification determinations from the U.S. Office of Government Ethics, and converted over 600 positions across the NIH to public filing status. On an annual basis, the incumbents of these positions now must make public disclosure of all positions with and income from outside activities.

5. Increasing the staffing of the NIH Ethics Office five-fold and selecting an experienced employee to lead this office so that the changes made to the NIH Ethics Program could be adequately administered and monitored.

6. Training all NIH employees (not just those required to receive training pursuant to applicable regulations) through live, interactive lectures on the conflict of interest laws and regulations.

7. Charging the Advisory Committee to the Director with the task of recommending awards for inclusion on a publicly available list after concluding that the award meets the regulatory definition of a bona fide award and therefore potentially eligible to be received by NIH employees.

8. Finally, working to create a comprehensive set of sweeping new conflict of interest regulations, which prohibit employment with companies and entities interested in or affected by the programs, operation, or policies of the NIH, holding stock in these companies (subject to a few narrowly tailored exceptions), and receipt of the cash component of all but the most prestigious awards for high level NIH officials. These sweeping new regulations bar these activities for at least one year to give the agency time to complete its review and strengthen its ethics oversight systems (including installing a state-of-the-art computer system), and to dispose of all pending investigations of past violations of NIH ethics requirements.

The NIH Director believes that these measures will safeguard the integrity of the intramural and extramural research at the NIH. Nevertheless, NIH will continuously evaluate these procedural protections, and make changes and additions as warranted.

Item

Human Embryonic Stem Cell Research – The Committee is very concerned that the current administration policy relating to human embryonic stem cell research is extremely limiting and is significantly slowing the pace of stem cell research. The Committee strongly believes that embryonic stem cells have the potential to be used to treat or cure the 100 million Americans who are afflicted with diseases such as cancer, heart disease, diabetes, Parkinson's, Alzheimer's, multiple sclerosis, spinal cord injury, and many others. While it originally appeared that 78 embryonic stem cell lines would be available for research under the Federal policy, now, more than 2 years after the President's announcement on August 9, 2001, only 24 are available to researchers. Moreover, scientists have told the Committee that all available stem cell lines were grown with mouse feeder cells, making their therapeutic use for humans uncertain. The Committee strongly urges the administration to modify the current embryonic stem cell policy so that it provides this area of research the greatest opportunity to lead to the treatments and cures for which we are all hoping. The Committee is also deeply concerned with the slow pace of implementation of the current policy. (p. 96)

Action taken or to be taken

The National Institutes of Health (NIH) continues to lead the federal effort in supporting human embryonic stem cell (hESC) research. To help make more hESC lines available, the NIH awarded nine "Human Embryonic Stem Cell Research Resource Infrastructure Enhancement Awards" that aid the providers' efforts to expand, test, perform quality assurance, freeze, store, and distribute hESC lines for research. As a result of these grants, 22 hESC lines are currently available for distribution to scientists worldwide. Providers of these lines have shipped more than 500 lines to scientists. To stimulate the research field, the NIH is supporting five hESC short-term training courses which enables scientist to learn stem cell culturing techniques.

NIH continues to support and conduct numerous research projects using hESCs and is also introducing new initiatives. In FY 2005, NIH is planning to fund two new initiatives, "Centers of Excellence in Translational Stem Cell Research" and the "National Stem Cell Bank." There is a compelling need to bring together teams of research scientists to translate these basic science advances in stem cell biology into animal model studies, and ultimately, Phase One Clinical Trials. As a result, the NIH will establish three Centers of Excellence in Translational Stem Cell Research where scientists will exploit new discoveries in basic embryonic and adult stem cell biology, translating them into animal model studies, with the goal of leading to new treatment strategies for diseases such as diabetes, Parkinson's disease, or cardiac disease. Also, the research community has repeatedly informed NIH that affordable and timely access to cell lines eligible for Federal funding, intellectual property considerations, and quality assurance are all pivotal considerations to moving the research agenda forward. To address these issues, NIH will establish a national repository and characterization center for hESCs — the National Stem Cell Bank. This extramural Bank would combine the functions of a cell repository with the expert capabilities and economies of scale of a research service center with the goal of enhancing the availability of the hESCs currently listed on the NIH Human Embryonic Stem Cell Registry.

With regard to the concern about exposure of cells to mouse feeder cells, the NIH Stem Cell Task Force and the NIH hESC infrastructure awardees met to discuss whether hESCs grown on human feeder layers could be used more readily and with greater safety than hESCs grown on mouse feeder layers. At that meeting, FDA representatives asserted that cell lines grown on human feeder layers are not necessarily safer for clinical trials than stem cells grown on mouse feeder layers. Either mouse or human feeder layers might harbor pathogens that could be transmitted to the hESCs grown on them. In either case, the FDA would evaluate a proposed clinical investigation prior to such a study proceeding. The FDA's evaluation would include information related to safety issues, such as the characteristics of the stem cells, how the stem cells were derived, the properties of any feeder layer used to propagate the cells, potential contaminants introduced through the media or sera used in culture, and the presence of infectious agents transmitted from feeder layer cells to cultured hESCs. It is important to note that there are living cellular products currently in clinical trials that have been developed using culture techniques that involve living animal cells. Thus, the FDA's regulatory approach does not preclude the development and clinical testing of cellular products from hESC lines grown on either mouse or human feeder layers as long as appropriate safety issues are addressed. Contact with feeder cells is one of many safety considerations that need to be assessed before clinical application of this technology.

One example of a safety consideration related to feeder layers was reported by Martin *et al*. in the January 2005 online edition of *Nature Medicine*. Many human beings have antibodies against the non-human sugar molecule called N-glycolylneuraminic acid (Neu5Gc) circulating in their blood. Scientists hypothesize that the antibodies are produced after a person is exposed to Neu5Gc in animal products consumed as food. NIH-supported scientists have now determined that human embryonic stem cells (hESCs) grown on mouse feeder cells and supported with animal-derived cell culture products express Neu5Gc on their cell surfaces. Cultured hESCs exposed to human blood serum were marked for destruction by the immune system. However, scientists do not yet know whether transplanted cells derived from these hESCs (such as insulin

producing cells or dopamine producing cells) would be destroyed by the immune system. This study identifies another safety concern that must be addressed before derivatives of hESCs could be used to treat patients in clinical trials.

Item

***Amnion-derived Stem Cell [ASC]* –** The Committee understands that ASC technologies offers the potential to develop and produce an adequate supply of cells for therapeutic cellular transplantation based upon isolation from placental tissue. The Committee supports all avenues of stem cell research and strongly urges the NIH to explore research in this area and steps necessary for the clinical application of this technology. (p. 162)

Action taken or to be taken

The NIH is actively supporting studies that investigate the use of all types of stem cells as potential human disease therapies, including studies of placental cord blood stem cells. The amnion and chorion surround the developing fetus *in utero*, and are expelled at birth along with the placenta. Currently, the majority of stem cell research using the human placenta is focused upon the blood contained within the placenta and the attached umbilical cord. Because the relatively small number of stem cells available in a single umbilical cord limits the use of cord blood transplants for adult patients and older children, NIH is supporting numerous investigator-initiated grants attempting to expand cord blood stem cells in the laboratory.

In addition, NHLBI is currently sponsoring two multi-center clinical trials using cord blood stem cells. One of these clinical trials is called the Cord Blood Transplantation Study (COBLT.) Information about COBLT can be found on its website at: http://spitfire.emmes.com/study/cord/. As part of this project, NHLBI has designated two cord blood banks to collect cord blood units. COBLT is testing whether cord blood stem cells can be used instead of bone marrow transplantation to treat children and adults with a variety of cancers, blood diseases, and genetic disorders. The study is also trying to determine whether cord blood stem cells are more readily accepted by the transplant recipient's bodies when the cells are less closely matched (a condition known as human leukocyte antigen, or HLA mismatch.) Preliminary results demonstrated that cord blood stem cells can engraft in leukemia patients and in some cases cure the disease. However, because each unit of cord blood contains only a limited number of cells, the transplants sometimes failed. Investigators began transplanting more than one unit of cord blood cells in leukemia patients and achieved greater success in curing the cancer. The investigators are now trying to determine a dose per weight limit that may predict successful transplant engraftment and cure of disease. The last patients were recruited to this trial by December 31, 2003, and the study is now in data analysis mode. Information gleaned from this important clinical trial will help scientists develop improved methods for the use of cord blood stem cells to treat human diseases.

A second NHLBI-sponsored effort established a national Sibling Donor Cord Blood (SDCB) Program, and evaluated its use in a multi-center pilot study of transplantation. Findings on related umbilical cord blood transplantation in patients with thalassemia and sickle cell disease were published in the March 15, 2003 issue of Blood. The authors analyzed 44 patients given a cord blood transplant from a sibling to treat either thalassemia (n = 33) or sickle cell disease (n =

11). The trial tested several different immune-suppression regimens. No children died and 36 of 44 remain free of disease, with a median follow-up of 24 months. The authors concluded that cord blood transplantation from a sibling donor to treat thalessemia and sickle-cell disease offers a good probability of success and is associated with a low risk of transplant rejection. Optimization of transplantation strategies could further improve these results. Patients are now being recruited to participate in a transplantation study.

Item

Autism Spectrum Disorders – The Committee is encouraged by the NIH's autism research matrix and urges NIH to devote sufficient resources to this research agenda. The Committee urges the NIH when implementing the autism research matrix to coordinate with autism organizations already funding research initiatives to ensure the most efficient use of it resources. The Committee also notes the promise of particular areas cited in the matrix, including genetic and behavioral characterizations of the disorder and screening and early diagnosis. (p. 162)

Action taken or to be taken

Please refer to House Significant Item on page OD-38, ***Autism Spectrum Disorders*** of this document for response to this significant item regarding NIH's autism research matrix.

Item

Autoimmune Diseases – The Autoimmune Disease Coordinating Committee, with representation from each NIH Institute, Centers for Disease Control and Prevention, Food and Drug Administration, Veterans Administration, and patient advocacy organizations, has been effective in fostering collaborative, integrated multi-Institute research on issues affecting the entire genetically related family of autoimmune diseases, as recommended in the Autoimmune Diseases Research Plan. This collaboration has been a significant factor in achieving recent advances in the understanding, diagnosis and treatment of autoimmune diseases. Congress supports the committee's continued efforts in implementing the Autoimmune Diseases Research Plan. (p. 163)

Action taken or to be taken

Please refer to House Significant Item on page OD-42, ***Autoimmune Diseases*** of this document for response to this significant item.

Item

Childhood Obesity, Trans-NIH Obesity Research Initiative – The committee encourages the NIH to further expand the Trans-NIH obesity research initiative to include a multi-center study of the metabolic, psychological, and genetic precursors of obesity in children. (p. 163)

Action Taken or To Be Taken

Childhood obesity has risen at an alarming rate, and individuals who are obese as children may face a lifetime of serious health problems. Thus, the NIH is propelling a range of new pediatric

obesity research efforts, from building an understanding of the complex causes of obesity that will help guide the development of new intervention approaches, to encouraging current design and testing of prevention and treatment strategies. These research avenues are consistent with the recommendations in the recently-released Strategic Plan for NIH Obesity Research. Among new NIH efforts to understand the precursors of obesity in children is a planned initiative to enhance mechanistic studies of the impact of the intrauterine and neonatal environment on the development of obesity and diabetes in offspring. Another effort is being planned to accelerate human obesity genetics studies; this research would complement ongoing investigations of genetic factors relevant to obesity in animal models. Also under development is a new effort to help build understanding of the neurobiological basis of obesity. The NIH is pursuing several new initiatives to augment research on prevention and treatment strategies for pediatric obesity. For example, a new trans-NIH effort is encouraging research to test childhood obesity prevention and treatment intervention programs that would be delivered in primary care practices. Through a complementary initiative, the NIH is soliciting research proposals to develop and test intervention approaches to prevention or management of pediatric obesity in a variety of other settings. Such settings could include the family/home, day-care or preschool, school, other appropriate community venues, or integrated cross-site studies. Another initiative is focused on school-based interventions to prevent obesity, encouraging investigators to develop and evaluate such intervention strategies. Associated with the escalation in childhood obesity is an alarming increase in type 2 diabetes in children. The NIH's NIDDK has launched the "Studies to Treat or Prevent Pediatric Type 2 Diabetes (STOPP-T2D)," a multi-site consortium that is developing clinical trials related to type 2 diabetes in children. These trials include a multi-center trial to compare three treatment approaches for type 2 diabetes (Treatment Options for Type 2 Diabetes in Adolescents and Youth, TODAY), and pilot studies to assess the feasibility of a planned school-based prevention trial. Analyses are also continuing of the NHLBI Growth and Health Study, designed to examine factors associated with the development of obesity, including environmental, cultural, and behavioral factors. This study led to the development of Girls health Enrichment Multisided Studies, GEMS, a multimember program of four pilot studies and two full-scale studies to develop and test interventions to prevent obesity by decreasing weight gain in high-risk African American preadolescent girls. Examples of other NIH research on childhood obesity include a study of body mass index rebound in childhood, an intervention study testing obesity prevention approaches in African American teens, and a study testing an intervention to modify home environments to promote healthful behaviors.

Item

Chronic Fatigue Syndrome [CFS] – The Committee is disappointed that NIH funding for CFS has basically remained flat in recent years, despite repeated congressional requests for increases. In addition, several grants represented to be for CFS research have limited direct relevance to CFS. The Committee notes that the Office of Research on Women's Health, through the Trans-NIH Working Group for Research on Chronic Fatigue Syndrome, is working on a request for applications [RFA] based on the findings of a June 2003 scientific workshop on CFS. The Committee strongly urges the NIH to fund this RFA as soon as possible. The Committee also urges the NIH to expand the involvement of intramural researchers in the study of CFS. (p. 164)

Action taken or to be taken

The ORWH in collaboration with a Trans-NIH Working Group for Research on Chronic Fatigue Syndrome (CFSWG) that is comprised of members from 16 different NIH ICs has developed an action plan to enhance the status of CFS research at the NIH. Actions taken include the issuing a Program Announcement, convening a scientific workshop to generate interest and ideas, and generating interest in CFS among scientists in the NIH intramural community.

The Program Announcement (PA-02-34) encourages innovative and interdisciplinary research that might explain how the various body systems interact to produce symptoms associated with CFS. A well attended and informative scientific workshop, *Neuroimmune Mechanisms and Chronic Fatigue Syndrome,* will provide the basis for a new interdisciplinary RFA that will be issued in FY 2005, simultaneously with the proceedings from the scientific workshop. The CFSWG will also renew Program Announcement PA-02-34 in FY2005 to include research topics from this scientific workshop.

The ORWH has also developed and sponsors a new intramural Scientific Interest Group on Scientific Integrated Medical Research. This interest group has begun to generate trans-NIH partnerships that can speed the translation of research findings into treatments for patients suffering with CFS. This activity complements the CFSWG, which has been primarily focused on extramural research. These collaborative initiatives will contribute to an improved understanding of CFS.

Item

Clinical Investigators **-** The Committee commends the Office of the Director for rapidly launching programs with loan repayment and for training clinical investigators and encourages NIH to maintain and expand these programs. These programs will be crucial for establishing the clinically trained work force that will translate the promising basic discoveries supported by NIH into clinical application to cure and prevent disease in American citizens. (p. 164)

Action taken or to be taken

The NIH continues its commitment to maintain and enhance the biomedical research workforce through grant awards and loan repayment programs for clinical investigators with support and appropriations from Congress.

Since the extramural loan repayment programs were launched in 2002 the NIH has sought to increase accessibility of these programs to clinical investigators by broadening eligibility to include qualifying research supported not only by the NIH, but also by non-profit institutions. As a result, the number of applications has increased steadily since Fiscal Year (FY) 2003. In FY 2003, the number of applications received nearly doubled the number received in FY 2002. This trend continued in FY 2004, with nearly 2,500 applications received, representing a 30 percent increase in applications from the previous year. NIH has been responsive to this increasing volume of applications by awarding loan repayment contracts to more than 50 percent of the applicants in FY 2004. These awards make pursuit of a clinical research career feasible to

some investigators who may have sought alternative careers to repay their educational debt. This enhancement to the clinical research workforce should lead to clinical application of the discoveries that will aid in curing and preventing diseases.

Item

Cystic Fibrosis – The NIH Roadmap identifies the re-engineering of the clinical research system as a top priority. One of the strategies that the Roadmap recommends to enhance clinical research is establishing clinical trials networks that share informatics and other technologies. These networks also should include a significant number of institutions, in order to facilitate efficient recruitment and rapid enrollment of trial participants. The Committee believes that there are important opportunities for collaboration between NIH and these existing clinical trials network and encourages NIH to pursue this potential collaboration. (p. 165)

Action taken or to be taken

Please refer to pages OD-50 of this document for the NIH response to this significant item regarding ***Cystic Fibrosis***.

Item

Digestive Disease Commission -- The Committee calls on the Director, in collaboration with the Secretary, to establish a national commission on digestive diseases composed of distinguished scientists and physicians who are experts in digestive diseases, digestive disease patient advocates and representatives of Federal departments, agencies or institutes providing support for research related to digestive diseases in order to (1) study the incidence, duration, and mortality rates of digestive diseases, as well as their social and economic impacts; (2) evaluate public and private facilities and resources, including trained personnel and research activities, for the diagnosis, prevention, and treatment of such diseases; (3) identify related disease management programs, including biological, behavioral, nutritional, environmental, and social programs; and (4) develop a long-range plan for the use and organization of national resources to effectively deal with digestive diseases. (p.165)

Action taken or to be taken

In response to the Committee's request, careful analysis has been given to the proposed concept. As a result, it is considered appropriate and useful at this time for the NIH Director to establish a national digestive diseases commission to develop a long range research plan whose scope is consistent with the mission of the NIH. With broad input from leading scientific experts both within and external to the NIH--as well as from individuals with personal or family knowledge of digestive diseases--this commission will develop a long range research plan that: (1) highlights the burden of digestive diseases on individuals and society; (2) provides examples of research advances that are generating new knowledge vital to understanding, treating, and preventing these diseases; and (3) recommends new and emerging opportunities for future NIH-funded research, which offer promise for reducing the burden of digestive diseases. The long range plan will also include research-related activities of the NIH with respect to digestive diseases, such as efforts in science-based information dissemination and public health education, as well as research training and career development. By focusing on the research mission of the

NIH, the commission's plan and recommendations to the NIH will thus serve as a guidepost for the agency in its future program development efforts to combat digestive diseases through research.

Item

Fragile X Pediatric Training - The committee encourages the Director to increase the number and size of institutional training grants to institutions supporting pediatric training and the number of grants for career development clinical research. (p. 166)

Action taken or to be taken

The NIH, through the NICHD, supports an extensive program of pediatric institutional and individual training grants that are available to scientists interested in Fragile X research and other developmental disabilities. The Children's Health Act of 2000 instructed the Director, NICHD, to "increase the number and size of institutional training grants to institutions supporting pediatric training" and also to "increase…the number of career development awards for health professionals who intend to build careers in pediatric basic and clinical research." In FY 2004, the NICHD obligated $20.3 million, approximately $2.7 million more than in FY 2003, to support pediatric research training through training grants and fellowships, as well as through the Research Career Award Program that includes the Institute's Child Health Research Career Development Centers. The NICHD will continue its efforts to encourage the appropriate utilization of these existing mechanisms for the training of clinical investigators with interests in Fragile X syndrome and related issues. These efforts are reported annually to Congress in the Pediatric Research Initiative report.

Item

General Clinical Research Centers – The Committee has supported expansion of the General Clinical Research Centers program within the National Center for Research Resources. Wherever possible, the Committee encourages the Director to utilize the GCRCs as the foundation of NIH Roadmap activities related to clinical research. Rather than establishing programs in isolation, the Committee believes that it will be both synergistic and cost-effective for NIH Roadmap clinical research programs to be sited in the GCRCs as practicable. (p. 166)

Action taken or to be taken

As a significant partner of the NIH Roadmap for medical research, NCRR's programs complement a variety of the NIH Roadmap initiatives. Many of the NIH Roadmap initiatives will be implemented using a variety of NCRR clinical research resources. The interdisciplinary nature of NCRR's existing clinical research resources provides a national network that can be leveraged to facilitate several of the Roadmap goals, including those under the theme of Re-engineering the Clinical Research Enterprise.

One of the NIH Roadmap initiatives is the establishment of Regional Translational Research Centers (RTRCs). These centers will increase interactions between basic and clinical scientists and provide sophisticated advice and resources to help scientists master the many steps involved in bringing a new product from the bench to medical practice. The major purpose of the RTRCs

is to supplement and extend existing infrastructure to overcome current obstacles to broad-based translational research on a regional and national scale. Relevant NIH-funded centers, such as GCRCs, may be included as appropriate as part of a more comprehensive plan to enhance translational research in a region.

Another NIH Roadmap initiative is the Multidisciplinary Clinical Research Career Development Program. This initiative is intended to produce new clinical research leaders who can cross the boundaries of their disciplines and draw upon the strengths of other fields. Seven awards have been made to medical or public health institutions to provide training for up to 15-20 health professionals at the post-graduate level. All seven awards were to institutions with GCRCs, which provided the clinical research infrastructure needed to compete successfully for the award and will provide the trainees the tools they need for their research.

The NIH Roadmap National Electronic Clinical Trials and Research Network (NECTAR) initiative has funded 12 contracts for bringing existing networks together both in governance and with informatics. In addition, the NIH Roadmap has funded an inventory of clinical research networks and their best practices for operation. Additionally, NCRR is gathering input from the GCRCs and other clinical research centers and their partners. This information will be used to assist the GCRCs in developing interoperability with academic institutions, hospitals, clinics, government agencies, NIH and foundation supported research and public health networks, pharmaceutical companies, and patient advocacy groups.

Item

Genomics—The Committee recognizes that while the NHGRI is the primary Institute for addressing the human genome sequence, other Institutes should also identify the role genomics and genetics play in the progression of specific diseases. For example, the Committee urges the Director to encourage the various Institutes, including the NIA, NIMH, and NINDS, to take advantage of advances in microarray technology. Utilization of this technology could lead to improved prevention and therapeutic intervention strategies for Alzheimer's and Parkinson's diseases, as well as autism, obsessive compulsive and bi-polar disorder. (p. 167)

Action taken or to be taken

Many NIH Institutes invest in genomics, given its tremendous promise for advancing research on a broad range of diseases and disorders and on the normal processes of development and aging. Microarrays, or "gene chips," have become increasingly common research tools. NINDS-funded researchers are using microarrays to understand the genetic pathways that guide nervous system development and to improve diagnosis for neurological diseases, including Parkinson's disease, brain tumor, ALS, epilepsy, traumatic brain injury, and stroke. NIMH-supported researchers are using microarrays to identify the multiple genes responsible for schizophrenia, major depression, bipolar disorder, and other major mental disorders. The NIA conducts and supports research, utilizing microarray technology, on the genomics of aging and of age-associated diseases, including Alzheimer's disease. These Institutes also help researchers access the latest microarray technology. In FY2004, NIMH released an RFA on gene profiling in mental disorders to support new or expanded use of the technology in studies of human postmortem brain tissue. The NINDS and NIMH support a Microarray Consortium that offers expression

profiling services to all NINDS and NIMH extramural investigators and makes all of the resulting data publicly available through web-based databases. The NIA, in conjunction with the Johns Hopkins University, has established a microarray facility that provides extramural researchers with access to cDNA arrays of the NIA mouse and human clone collections at an easily affordable price.

The NIH supports the development of many other genomic tools and resources that will enable researchers to dissect the role of genes in diseases and ultimately develop treatments. In June 2004, the NIH Chemical Genomics Center was established as part of the NIH Roadmap's Molecular Libraries Screening Center Network (MLSCN). This Center is the first component of a nationwide consortium that will produce innovative chemical tools for use in biological research and drug development, in both the public and private sectors. The NIMH continues to support the Center for Genetic Studies on Mental Disorders, which provides the scientific community with genetic and genomic resources to be used in research on schizophrenia, bipolar disorder, depression, autism, attention deficit hyperactivity disorder, and autism. In 2004, the NIMH provided support for expanding a centralized molecular genetics facility based at Johns Hopkins University that provides high throughput genotyping and statistical genetics services for investigators seeking genes that contribute to human diseases. The NIA has established the National Repository for Alzheimer's disease, under the Alzheimer's Disease Genetics Initiative, for the large scale collection, longitudinal follow up, and analysis of the genetic bases of Alzheimer's disease.

Item

Graduate Training in Clinical Investigation Awards – In an effort to reverse the shortage of well-trained clinical investigators, Congress authorized the Clinical Research Curriculum Awards and the Graduate Training in Clinical Investigation Awards. The Curriculum Awards were intended to support institutional training programs in clinical research, with the second award intended to provide tuition and stipend support for enrolling students. For 3 consecutive years, this Committee has expressed concern that NIH has not moved forward with implementation of the Graduate Training in Clinical Investigation Awards. The Committee believes that NIH is compromising the effectiveness of the training programs that have been established through the Curriculum Awards by failing to fund the complementary student stipend/tuition awards. The report of the General Accounting Office on NIH implementation of the clinical research legislation substantiated the Committee's concerns. The Committee urges the Director to consider including these awards in the NIH Roadmap activities related to enhancing the clinical research workforce and provide sufficient funds to support 200 students in fiscal year 2005. (p. 167)

Action taken or to be taken

Graduate Training in Clinical Investigation was specifically authorized by the Clinical Research Enhancement Act, Public Law 106-505. Awards made under this authorization provide for research training and career development experiences for clinicians while they are pursuing master's or doctoral degrees relevant to clinical investigation. The Act describes the award as providing stipend, tuition, and institutional support. While not specifically called the Graduate Training in Clinical Investigation Award, a number of NIH Institutes and Centers support

programs designed to meet the objectives of the Clinical Research Enhancement Act. These programs provide stipend/salary and tuition support, and in all cases permit recipients to earn degrees in relevant areas of research. Several of these opportunities are described below.

In November 2001, the National Center for Research Resources announced the Mentored Clinical Research Scholar Program (K12), to provide support for clinician training to become independent, patient-oriented researchers. This program currently supports 95 individuals. In FY 2003, the National Eye Institute (NEI) implemented the NEI Institutional Clinical Scientist Development Program (K12) to provide support to develop clinical investigators to conduct vision-related research. Three awards have been made that will initially support 6 clinician scientists, each for a two- to five-year period. The National Institute of Diabetes and Digestive and Kidney Diseases has just announced a complementary Institutional research training (T32) and clinical scientist career development program (K12) to provide an integrated program to prepare pediatricians for careers in pediatric endocrinology research related to diabetes. In FY 2004, the National Institute of Child Health and Human Development (NICHD) initiated the Pediatric Critical Care Scientist Development Program, a new career development program for pediatric critical care, and in FY 2005, the NICHD plans to support a Men's Reproductive Health Clinical Research Career Development Program. Lastly, the NICHD is leading one of the NIH Roadmap initiatives to reinvigorate the clinical research enterprise. As part of the initiative, an announcement for Multidisciplinary Clinical Research Career Development Programs was issued in FY 2004, for the support of the early career development of clinical researchers from a variety of disciplines engaged in all types of clinical research, including patient-oriented research, translational research, small- and large-scale clinical investigation and trials, and epidemiologic and natural history studies. In FY 2004 this program began with 7 awards and a total of 40 funded career development positions. In FY 2005, it is expected that it will continue to ramp up and will support a total of 115 individuals engaged in career development experiences in clinical investigation.

All of these awards have been developed to meet the objectives of the Clinical Research Enhancement Act. These programs have spawned numerous Masters-level advanced clinical research degree programs which are available to clinicians interested in pursuing academic research. The expectations described for the Graduate Training in Clinical Investigation Awards have been vastly exceeded by the NIH response to the Clinical Research Enhancement Act. Nevertheless, we will continue to emphasize the need for graduate training as it relates to patient-oriented research in order to ensure that the nation's needs for clinician researchers are met.

Item

Heart Disease, Stroke and Other Cardiovascular Diseases- The Committee recognizes that the problems associated with heart disease, stroke and other cardiovascular diseases involve many institutes and centers, including NHLBI, NINDS, NIA, NIDCR, and NCRR. The Committee strongly urges the Director to expand its research portfolio and increase its resources and better coordinate cross-cutting research on these diseases in all institutes, centers and divisions, as appropriate, and through all available mechanisms. The Committee requests the Director to be prepared to report on initiatives on these diseases begun in fiscal year 2004 or scheduled to begin in fiscal year 2005 at the fiscal year 2006 appropriations hearings. (p. 167)

Action taken or to be taken
Please refer to pages OD-44 of this document for response to this significant item regarding "***Heart Disease, Stroke and Other Cardiovascular Diseases".***

Item
Hepatitis B— the Committee is aware that although there has been tremendous success in the prevention and treatment of hepatitis B, this disease remains a serious concern. The large number of immigrants to the United States from countries where hepatitis B is endemic will keep the disease in the forefront of public health for years to come. The Director of NIH is urged to make hepatitis B a priority and to stimulate research to find complements for the current therapies; improvements in prevention, detection and treatment; and develop new vaccines and outreach programs. (p. 167)

Action taken or to be taken
While rates of hepatitis B have declined in the United States in recent years, it remains a major cause of chronic hepatitis, cirrhosis, and liver cancer in this country and worldwide. Certain groups in the U.S. population are at high risk of becoming infected with the hepatitis B virus, such as recent immigrants from countries where hepatitis B is endemic. To combat the human consequences of hepatitis B, the NIH remains committed to supporting and conducting research that will yield improvements in prevention, detection and treatment of hepatitis B. Several NIH Institutes and Centers support research on hepatitis B including the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the National Institute of Allergy and Infectious Diseases (NIAID), and the National Heart, Lung, and Blood Institute (NHLBI).

The NIDDK currently supports ongoing intramural and extramural research efforts to identify new, more effective approaches to therapy of hepatitis B, including testing combinations of antiviral and immunological agents, some as complements to already approved hepatitis B therapies. Additionally, a recent trans-NIH planning process to develop an "Action Plan" for liver disease research to be pursued over the next decade highlighted several important research goals related to developing better approaches to therapy of hepatitis B, including identifying new targets in the virus and patient for drug design, understanding why current antiviral treatments fail to completely eradicate the virus, and testing new approaches such as drug combinations. To better understand the current state of science on hepatitis B research, NIDDK will sponsor a meeting on this subject, which is tentatively planned for late 2005 or early 2006.

NIAID-supported investigations of the host immune responses to the hepatitis B virus (HBV) and how the virus attempts to circumvent the responses are yielding important information on the mechanisms of hepatitis B pathogenesis. For example, NIAID-supported researchers are investigating the mechanisms by which the host clears the HBV infection and the relationship of these mechanisms to clinical disease, which may provide clues to new preventive and therapeutic measures for hepatitis B. Additionally, NIAID supports an *in vitro* antiviral screening program to identify new HBV therapies and is actively pursuing public-private partnerships to encourage the development of treatments aimed at novel targets for hepatitis B. The NIAID solicitation for

"Animal Models for the Prevention and Treatment of Hepatitis B and Hepatitis C", slated for funding in FY2005, will continue the opportunity for preclinical evaluations of new drug candidates or therapy combinations for hepatitis B.

To improve the detection and control of hepatitis B, the NHLBI currently supports research to develop an assay for screening organ donors for hepatitis B. NHLBI-supported research is also under way to develop an inexpensive, simple, high-performance dipstick test to detect hepatitis B surface antigen for use in resource-limited settings. This technology could aid hepatitis B control in developing countries, where, despite the high carrier rate of hepatitis B, the blood supply is generally not screened for the virus because currently available tests are too costly. Lastly, in May 2004, the NHLBI sponsored a Working Group on Global Blood Safety attended by national and international experts in transfusion medicine who recommended that centers of excellence in transfusion medicine be established in resource-limited countries. The NHLBI is exploring the feasibility of expanding an existing blood safety research program to include regions of Africa, Asia, and Latin America. Options are being explored to study HBV and other new and emerging infectious agents in the blood supply of selected international sites.

The NIH and other Federal agencies are also engaged in outreach programs to educate the public about the risks of hepatitis B and post-infection management. For example, the National Digestive Diseases Information Clearinghouse (NDDIC) supported by the NIDDK prepares publications on hepatitis B such as "What I need to know about Hepatitis B." This publication is available online to the public in both English and Spanish. The Centers for Disease Control and Prevention (CDC) also has several online educational publications on hepatitis B targeted to the general public, including "Prevent Hepatitis B: Get Vaccinated" and "Living with Chronic Hepatitis B." The CDC also provides interactive online programs for use by health care professionals such as "Hepatitis B and Refugees: A Clinical Perspective."

Item:

High-Risk Research – As the NIH enters into a period of limited funding resources, the peer review system will naturally tend to reward conservative research proposals rather than bolder ideas that have a higher risk of succeeding. The Committee strongly urges the NIH to beware of this tendency, in terms of both the research grants that it awards and the types of researchers who receive them. Relying solely on tried-and-true approaches to medical research, conducted solely by veteran, established researchers, will not result in quantum leaps in discovery. Despite the current decline in the growth rate of NIH's budget, the NIH must continue to fund high-risk research and young investigators who have innovative ideas. (p. 168)

Action taken or to be taken:

In 2004, as part of the Roadmap, NIH initiated the NIH Director's Pioneer Award program. The purpose of this new funding mechanism is to support researchers of exceptional creativity who propose "pioneering" approaches to major contemporary challenges in biomedical science. Nominees submitted a brief essay summarizing their vision for how they believed they could make seminal contributions to an important problem, along with a biographical sketch and letters of reference. Nominees were evaluated on their innovation, creativity, and potential for future groundbreaking research; their motivation and intellectual energy; and the relevance of the

research and impact on NIH's mission. The procedure for evaluating applicants was distinct from the traditional NIH peer review, "study section" process and was based on review of the individual's potential to make seminal contributions toward solving an important biomedical research problem. The evaluation process featured a shorter turnaround time and, at the last stage, interviews by a panel of outside experts. Nine highly creative investigators received NIH Director's Pioneer Awards of $500,000 direct costs for five years.

In 2005, nominations will again be solicited for the NIH Director's Pioneer Award program, and it is expected that 5-10 new awards will be made. However, to encourage pioneering research by newer, less established investigators, nominations will only be accepted for individuals who received their terminal doctoral degree within the last 15 years. NIH expects to continue announcing this program for at least the next several years.

In addition to the Pioneer Award program, innovation is a standard review criterion for each research application that NIH reviews. Reviewers are asked to carefully consider innovation and make sure that it is an integral part of the assessment of scientific merit.

Item

Human Tissue Supply – The Committee remains interested in matching the increased needs of NIH grantees, intramural, and university-based researchers who rely upon human tissues and organs to study human diseases and search for cures, including for those researchers dedicated to the study and cure of rare diseases. The Committee is aware that one of the leaders in this competitive field, the National Disease Research Interchange [NDRI], is uniquely positioned to obtain this valuable and effective alternative research resource. More than 500 peer-reviewed research advances made by NDRI-dependent researchers have been published during the past 4 years contributing to the research community's fund of knowledge. The Committee is encouraged by NDRI's role in these research advances and applauds the Director's expanded support for NDRI by bringing NEI, NIDDK, NIAID, NIAMS, and the Office of Rare Diseases into the multi-institute initiative. While this is promising, more needs to be done to match the demand for the use of human tissue in research. The Committee, therefore, strongly urges the Director to increase the core support NDRI receives from NCRR, and the Institute Directors to identify and implement program-specific initiatives intended to expand support for NDRI. (p. 168)

Action taken or to be taken

The National Disease Research Interchange (NDRI) is one of many U.S. groups that serve as brokers of human tissue for basic laboratory research. Approximately two-thirds of NDRI activity is supported by private foundations and fees charged to for-profit corporations. The remaining one-third of the activity is supported by the cooperative agreement, Human Tissue and Organ Resource for Research (HTOR), now in its fourteenth grant year. Such an award is based on periodic peer review and receives substantial guidance from the NIH staff. The NDRI cooperative agreement underwent a successful competitive review on June 30, 2003.

NCRR provided sole support during the first 8 years of the grant. However, in FY 1999 several additional NIH components, after being contacted by NCRR, provided co-funding. In FY 2004 a

total of $1,196,993 was provided to HTOR. Contributing IC's were: NEI ($200,000), NIAID ($150,000), NIDDK ($50,000), NIAMS ($25,000), the Office of Rare Diseases ($75,000) and NCRR ($696,993).

A total of 6,458 tissues were shipped by HTOR to investigators last year. Approximately 56 percent of the investigators used these tissues in basic research studies that were funded by NIH categorical Institutes: NEI, NIAID, NIDDK, NIAMS, NICHD, NHLBI, NCI, NINDS, NIA, and other Institutes. The remaining HTOR-brokered tissues are provided to researchers and companies who do not receive NIH funding.

Item

Liver Disease and the Veterans Health Administration – The Committee believes that closer collaboration with the Veterans Health Administration will significantly facilitate, accelerate, and leverage research to develop more effective treatments and cures for liver disease. The Committee notes that the Veterans Health Administration [VHA] has developed a significant database of veterans with hepatitis C that includes demographic, diagnostic, laboratory, drug treatment and co-morbidity population statistics that could be used to support a large number of NIH funded research efforts. The Committee is pleased that NIDDK, as the lead NIH Institute, has begun efforts to develop a cooperative agreement with the Veterans Health Administration as a vehicle for cost-sharing collaborative efforts to facilitate liver disease research on a trans-NIH basis. The Committee requests the Institute be prepared to report at the fiscal year 2006 Appropriation the progress and status of cooperative research efforts with the VHA to address hepatitis C. (p. 169)

Action taken or to be taken

The leadership of NIDDK and NIH agree that the Veterans Health Administration offers a rich resource for patient-oriented research in hepatitis C. A productive working relationship has been established with VHA, as evidenced by co-sponsorship of a recent NIH conference on hepatocellular carcinoma, and several meetings between VHA investigators, VHA hepatitis C program staff, and representatives of various institutes at NIH, including the NIDDK and the National Cancer Institute. A number of VA-based investigators working in the area of liver disease and viral hepatitis in particular are supported by NIH research grants. There is not currently in place a specific collaborative agreement for cost sharing, but this is one of a range of mechanisms to be explored in finding the best approach to collaboration between NIH and VHA. As we continue to explore these various options, NIH will be guided primarily by the quality of the scientific work proposed, the experience and expertise of the investigators involved, and the likelihood that the research will lead to new knowledge that will improve hepatitis care. An important resource that outlines future directions for research on liver disease, including hepatitis C, is the recently completed NIH *Action Plan for Liver Disease Research*. The objective of this Plan is to advance research on liver disease with the aim of decreasing the burden of liver disease in the United States. The Plan includes opportunities for collaborations with other Federal Agencies, including the VHA, as well as private foundations, and industry.

Item

Lymphatic System Research – Despite the central role of the lymphatic system in human health and disease, this focus of research and medical care has, until recently, been relatively neglected. The lack of research has created barriers to effective delivery of health care and limited the interest of biomedical investigators to pursue prospective studies in this area. Therefore, the Committee urges the Trans-NIH Coordinating Committee for the Lymphatic System to work with its member ICs to implement a comprehensive lymphatic research awareness campaign that is designed to target academia, governmental agencies, industry, scientific and medical professional organizations, and the public at large. (p. 169)

Action taken or to be taken

Please refer to page 51 of this document for response to this significant item regarding ***Lymphatic System Research.***

Item

Lymphatic System Research – The Committee also urges the OD to consider targeted initiatives regarding the lymphatic system, such as: (a) the development of suitable reagents, including monoclonal antibodies, to facilitate lymphatic investigation in vitro and in vivo; (b) the development of transgenic and knockout animal models; (c) the functional imaging of the lymphatic system; (d) academic career development; and (e) a national patient registry and tissue bank for lymphatic diseases. Finally, the Committee encourages the Coordinating Committee to work with the Center for Scientific Review and ICs to ensure that experts in the lymphatic system are adequately represented on peer review panels. (p. 169)

Action taken or to be taken

Please refer to pages OD-51 of this document for response to this significant item regarding "***Lymphatic System Research".***

Item

Minority Health and Racial Disparities – The Nation has invested greatly in the NIH providing tremendous opportunities for accelerated improvements in health and quality of life. Research advances must be applied more expeditiously to ensure greater improvements in health outcomes across all communities of color and the general public. The Committee strongly urges the NIH to improve, strengthen and expand its systems of information dissemination and outreach to health care providers, minority organizations, and the public. Knowing that one-size does not fit all as it relates to the public, communities, and the Institutes and Centers, the Committee strongly urges the Director of NIH, and the director of each of the Institutes and Centers (ICs) to report on their respective improved systems across these areas during next year's appropriations hearings. (p. 170)

Action taken or to be taken

The NIH ICs are committed to educating minority patient populations on disease management and quality care. The ICs plan to increase the number of culturally relevant health educational materials and to develop and expand linkages with minority organizations and professional

societies to increase dissemination of research advances to minority-serving institutions and minority communities. Some examples of these efforts include:

The **National Institute of Allergy and Infectious Diseases** (NIAID) will produce a series of low-literacy fact sheets on sexually transmitted infections, HIV/AIDS, and tuberculosis. NIAID will expand its distribution of these products to appropriate audiences.

The **National Institute of Nursing Research** (NINR) will continue its collaborations with the National Center on Minority Health and Health Disparities (NCMHD) to fund 17 Nursing Partnership Centers to Reduce Health Disparities between schools of nursing and minority-serving institutions to facilitate nurse scientist collaboration, increase research on health disparities, and enhance the development of minority nurse researchers.

The **National Institute of Neurological Disorders and Stroke** (NINDS) expanded its health education program, *Know Stroke. Know the Signs. Act in Time.* to populations at high risk for stroke - African Americans, Hispanics and seniors - in communities that have the health care systems in place to treat them.

The **National Cancer Institute** (NCI) will develop tools to support providers with new information in cancer care, communications with patients, and competencies in working with diverse populations. NCI will also address obesity and exercise in African American and other minority and underserved populations through effective dissemination of evidence-based energy balance intervention approaches.

The **National Heart, Lung and Blood Institute** (NHLBI) is expanding a number of efforts to educate health professionals, patients, and communities about preventing and controlling cardiovascular disease. NHLBI's community outreach efforts will disseminate to African Americans, American Indians, and Latinos cardiovascular health materials to help them recognize risk factors, seek appropriate treatment, and adopt healthy lifestyle behaviors.

The **National Center on Minority Health and Health Disparities** will develop community-based research programs focused on preventing disease and eliminating barriers to effective health care for relevant racial and ethnic minority and other health disparity communities.

The **National Institute of Arthritis and Musculoskeletal and Skin Diseases** will expand its Spanish-language Web site to include the newly developed and/or translated health information and will translate publications in languages other than English in print and electronic formats.

The **National Center for Complementary and Alternative Medicine** (NCCAM) will employ multimedia technology, such as Web Chats, teleconferences, and minority-focused media to disseminate CAM information.

The **Fogarty International Center** (FIC), in partnership with the NCMHD, will increase its outreach efforts to minority medical and public health students to increase application to the FIC-

Ellison Medical Student program. FIC will also work with the NCMHD to support activities to improve the health of indigenous people as part of the NIH agreement with Canada.

The **National Library of Medicine** (NLM) has a strong emphasis on supporting efforts to use health information and information technology to reduce and eliminate health disparities in minority communities. NLM supports education and training of minorities in biomedicine and health sciences librarianship, local projects carried out by community-based organizations and reliance on the National Network of Libraries of Medicine to support this work throughout the country.

Other activities are taking place in Office of the Director, National Eye Institute, National Human Genome Research Institute, National Institute on Aging, National Institute on Alcohol Abuse and Alcoholism, National Institute of Biomedical Imaging and Bioengineering, National Institute of Child Health and Human Development, National Institute of Deafness and Communication Disorders, National Institute on Dental and Craniofacial Research, National Institute on Drug Abuse, National Institute of Environmental Health Sciences, National Institute of General Medical Sciences, National Institute of Mental Health, National Center for Research Resources, and the Clinical Center.

All NIH Institutes and Centers will be prepared to discuss their initiatives at the hearings.

Item

Office of Dietary Supplements – The Committee continues to strongly support the important work of this Office. Use of dietary supplements has increased significantly among Americans who want to improve their health and prevent disease. There is a great need for additional research to better inform consumers of the health benefits of supplements. Accordingly, the Committee has provided additional funds to expand this office's efforts. In particular, the Committee expects the ODS to speed up ongoing collaborative efforts to develop, validate and disseminate analytical methods and reference materials for the most commonly used botanicals and other dietary supplements. The Committee also expects the ODS to contract with industry non-profit associations or foundations which currently have and maintain a database of dietary supplement labels to develop, create, continually update, maintain and make available to Government and research entities a database of all supplement labels sold in the United States. The creation of this database would allow ODS to have access for research purposes of all known supplements manufactured in the United States and to allow access by other Federal agencies for ensuring safety to consumers, through the mandatory listing of ingredients in these products on the label, who purchase supplements manufactured and/or sold in the United States. (p. 170)

Action taken or to be taken

In 2002 the Office of Dietary Supplements (ODS) created a program of analytical methods and reference materials to coordinate activities among Federal agencies, non-governmental organizations, academia, and the private sector. Methods development activities include collaboration with the USDA as well as contracts with small businesses for methods development. The main methods validation effort uses an Interagency Agreement with the Food

and Drug Administration to fund a contract with AOAC International, the scientific society devoted to validation of analytical methods. The program is now entering year 3 of a 5-year plan to validate methods for dietary supplement ingredients. The program initially called for the development of 20 methods over 5 years. ODS has accelerated this program so that in its third year there are 38 methods in various stages of development and validation. A lack of analytical standards has historically hindered methods development and validation that has led ODS to modify its program to include the production of analytical standards. ODS has provided analytical standards for development and validation of methods for St. John's wort, valerian, cranberry, blueberry, bilberry, and pyrrolizidine alkaloids. It has also provided the United States Pharmacopeia monograph program with several reference standards: gingerol (for ginger), eleutheroside B (for Eleuthero), and beta-sitosterol (for saw palmetto and several other plant monographs). Development of analytical standards for hydrastine and berberine (for goldenseal) is in progress. In addition, ODS has a 5-year Interagency Agreement with the National Institute of Standards and Technology. The agreement originally called for production of 6-8 sets of botanical Standard Reference Materials (SRM) by the end of 5 years. In the third year of the program, there are 9 sets of botanical SRMs in varying stages of development or production.

In response to the current Report language, ODS has met with industry non-profit foundation representatives to explore existing resources pertinent to developing a comprehensive, updated label database. ODS is developing a request for proposals and intends to contract for such a database in order to meet the research requirements of ODS as well as other Federal agencies and the scientific community.

Item

Office of Science Education – The Committee is pleased with the work of the Office of Science Education and encourages all of the NIH Institutes to work with the Office to support supplemental curricular and training project for K-12 science education. The support from the NIH Institutes and centers greatly enhance the capacity of this Office to provide the critical investment in science literacy among young people throughout the Nation.
(p. 171)

Action taken ot to be taken

The Office of Science Education thanks the Committee for their recognition of the *NIH Curriculum Supplements* and related professional development activities. These efforts are aimed at improving K-12 science education in schools nationwide. To date, over 140,000 supplements have been distributed, each in response to a teacher's request. 3,000 of these teachers have attended NIH training sessions and up to 50,000 individuals a month access NIH educational resources on the OSE Web site, http://science.education.nih.gov. As the Committee recognizes, the NIH institutes and centers are essential partners in developing these educational resources. OSE will continue with these partnerships to support our nation's teachers as we work towards our ultimate goal: to improve science literacy for all Americans.

Item

Office of Research on Women's Health - The Committee recognizes the critical role played by the Specialized Centers of Research on Sex and Gender Factors Affecting Women's Health and encourages the Office to continue programmatic initiatives to further this work. The Committee also supports the development of an intramural women's health program at NIH. (p. 171)

Action taken or to be taken

ORWH, with several NIH institutes and the Food and Drug Administration (FDA), funded eleven Specialized Centers of Research (SCOR) centers in FY 2002. These interdisciplinary research centers have proved successful in mobilizing scientists of diverse disciplines to bring together their expertise to focus on examining how sex and gender factors contribute to health and disease. The ORWH will continue to fund these interdisciplinary collaborations. This effort will be instrumental in continuing this innovative interdisciplinary research approach to women's health research and sex and gender factors among seasoned extramural scientists. A new RFA will be developed in FY 2006 and funded in FY 2007 to continue the SCOR Centers or fund new ones. SCORs are providing new models for unique opportunities for collaborations and networking across different centers through mutual scientific interests to enhance scientific opportunities.

The ORWH/NIH Intramural Program on Research on Women's Health's (IPRWH) successfully established an innovative interdisciplinary program that serves as the focal point for all women′s health research, including sex and gender comparisons. The mission is to: 1) Promote, stimulate, and support efforts to improve the health of women through biomedical and behavioral research within the NIH IRP; 2) Enhance communication among, and recruitment of researchers on women's health and the health of women and men through sex and gender comparisons among the Institutes and Centers; and 3) Enhance interdisciplinary research through the development of specific training programs and recruitment of new clinical and basic research trainees into the IPRWH at the NIH. An innovative, shared post-doctoral fellow program in women's health research is being developed currently in the intramural program. This training program will, for the first time, enable and facilitate excellent, collaborative inter- and multidisciplinary research in the area of women's health and sex/gender factors in the intramural community.

Item

Pediatric Research Initiative- The Committee urges the Office of the Director to expand the Pediatric Research Initiative, as authorized by the Children's Health Act of 2000. The Committee strongly supports the growth of support for pediatric research across Institutes and encourages activities which stimulate new and promising areas of pediatric research. Additionally, the Committee urges NIH to collaborate with the CDC and HRSA in research areas related to heritable and genetic disorders affecting children. (p. 171)

Action taken or to be taken

NIH has continued to fund new and expanded pediatric research through an array of individual IC initiated activities. The details of these activities have been summarized in several reports to Congress. An updated report that describes FY 2004 activities included under the Pediatric Research Initiative will be submitted in the spring of 2005.

As a part of its own effort to enhance new directions in pediatric research, the NICHD continues to provide NIH leadership in developing new newborn screening and diagnostic technologies and in developing the infrastructure to permit wider use of these important tests. The NICHD is taking the lead on developing the evidence base to inform the Secretary, DHHS, as well as state and federal policy makers regarding newborn screening. The NICHD also continues to work with HRSA and the CDC, among others, to sponsor joint scientific conferences and training and professional development programs; and to explore the complex genetic, medical, technological, legal and ethical issues associated with newborn screening.

Item

Prader-Willi Syndrome – The Committee commends the NIH for creation of an Obesity Research Task Force and for NIH's recognition of the need to prevent and treat obesity beginning in childhood. However, the committee strongly urges the Task Force to explicitly include, across the six proposed trans-NIH obesity initiatives, investigations into the genetic causes of obesity beginning with study of Prader-Willi Syndrome. Furthermore, the Committee urges the Director of NIH to conduct outreach to the Prader-Willi Syndrome community to participate in research at the proposed "Obesity Clinical Research Center." The NIH should be prepared to report on the progress made by the Obesity Research Task Force, and the trans-NIH research efforts to appropriately incorporate both children and genetics into the overall obesity research agenda during the fiscal year 2006 appropriations hearings. (p. 172)

Action taken or to be taken

The NIH is pursuing several avenues of research on Prader-Willi Syndrome (PWS). For example, in the area of genetics, the NIH supports genetic and clinical studies on the imprinted genes underlying PWS, including genes causing obesity. The NIH also supports the Human Genetic Cell Repository, which contains a collection of cell lines from individuals with PWS and from unaffected family members; this resource will facilitate future research. In other areas, the NIH supports research that is elucidating the metabolic underpinnings of this serious disease. Such research complements genetic studies and may also help illuminate the functions of genetic factors that contribute to PWS. NIH-supported research has demonstrated that children with PWS have very high fasting levels of the hormone ghrelin, and more recently showed that treatment with octreotide, an agent that inhibits gut peptide secretion, suppressed fasting gherlin levels in children with PWS. Although it is not yet known whether octreotide treatment will change eating behavior and promote weight loss, these results demonstrate the importance of basic research in identifying potential therapeutic targets for subsequent clinical studies. NIH intramural scientists have conducted neuroimaging studies using Positron Emission Tomography (PET) to compare the differences in the architecture of the brain in individuals with and without PWS. It is planned that the new intramural Obesity Clinical Research Center, which is under development, will foster multidisciplinary approaches to obesity research in areas such as

genetics, metabolism, endocrinology, nutrition, cardiovascular biology, gastroenterology, hepatology, and behavioral sciences. Other NIH-supported research focuses on topics such as compulsive food seeking and food motivation in individuals with PWS, as well as the dietary management of chronic conditions of childhood, including PWS. In addition to recognizing the importance of continued research on PWS, the NIH also shares the Committee's concern about childhood obesity more broadly, and is intensifying research on childhood obesity and obesity genetics.

Item

Public Health Relevance of Research Awards – The Committee is encouraged by steps the [NIH] is taking to improve communications regarding the public health relevance of its research awards. Specifically, the Committee is pleased NIH has proposed a modification to its standard grant application, PHS Form 398, requiring all grantees to include a statement of public health significance. The Committee urges the Department of Health and Human Services and the Office of Management and Budget to approve the proposed revision and support the agency in its efforts to implement this important change in the grant application form. (p. 172)

Action taken or to be taken

Please refer to page OD-34 of this document for OD/OER's response to this significant item regarding ***"Public Health Relevance of Research Awards***".

Item

Rare Liver Diseases – The Committee is pleased that the Office of Rare Diseases has provided significant co-funding, along with NIDDK, for the Biliary Atresia Research Network. The Committee urges ORD to continue to address rare liver diseases including primary biliary cirrhosis, primary sclerosing cholangitis, and auto-immune hepatitis. (p. 172)

Action taken or to be taken

ORD continues to support the Biliary Atresia Research Network. In addition, as part of the Rare Diseases Clinical Research Network, ORD, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), and the National Center for Research Resources (NCRR) support the development of a coordinated and integrated Cholestatic Liver Disease Consortium. The consortium will include nine sites in the United States, each with investigators who have extensive clinical experience, patient populations, and research programs for these disorders, and each with a General Clinical Research Center (GCRC). The consortium will initially focus on investigations of five rare, genetic causes of intrahepatic cholestasis including PFIC (progressive familial intrahepatic cholestasis), bile acid synthesis defects, Alagille syndrome, alpha-1-antitrypsin deficiency, and mitochondrial hepatopathies. These disorders have serious if not fatal consequences without liver transplantation and severely affect children's normal growth and development. Collaboration with the support/advocacy groups for these rare liver disorders will be integrated into the consortium at all levels.

ORD is also an active collaborator with the National Institute of Diabetes, and Digestive and Kidney Diseases and other NIH Institutes and Centers in the development and implementation of the trans-NIH Action Plan for Liver Disease Research. ORD's special interest is in autoimmune

liver diseases including primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis all of which can be severe, progressive and can lead to death from end-stage liver disease; pediatric liver diseases including biliary atresia and cholestatic liver disease; and genetic liver diseases including cystic fibrosis and polycystic liver diseases. The goal of the Action Plan for Liver Disease Research is to advance research on liver diseases with the aim of decreasing the burden of liver disease in the United States.

Item

Saliva Research **-** The Committee has learned that saliva is gaining value as a diagnostic tool and potential monitor of disease progression in systemic disorders, including Alzheimer's disease, Sjögren's syndrome, cystic fibrosis, and diabetes; moreover, studies have uncovered the presence of a cancer-related protein whose concentration increases in the presence of breast cancer--thus, having the potential as a diagnostic marker for the early detection of breast cancer. The Director of NIH is urged, working with the NIDCR, to find ways to expand and accelerate research in this area and report back to the Committee prior to next year's hearing. (p. 172)

Action taken or to be taken

In 1999 the NIDCR started a dialogue with NCI, NHLBI, NIAID, NIAAA and NIAID, which led to a workshop on salivary-based diagnostic technologies and an initiative in this area thereafter. As a result of this initiative, the NIDCR has launched a program for the development of saliva-based diagnostic technologies. Some of the investigators in the program are focusing on the fabrication of a portable device for oral fluid-based diagnostics. It integrates microchip-based immunoassays with miniaturized power supplies, reagent cartridges, miniaturized laser-induced fluorescence detector, and control hardware for the detection of biomarkers associated with oral and systemic diseases, such as cardiovascular disease. Other investigators focus on the development of an integrated micro-fluidics platform. This device will be able to detect HIV, hepatitis, early signs of breast and oral cancers, various hormones, or monitor patients undergoing kidney dialysis. The NIDCR is planning to continue the program for another five years to promote the fabrication and validation of these platforms. It is at that stage that the Institute will consult with other Institutes, including NCI, for clinical evaluation of these technologies.

In order to complement the Salivary-Based Diagnostic Technologies program, particularly the validation of diagnostic technologies, in FY 2004, the NIDCR created a program to catalogue and characterize the proteins present in human saliva (the human salivary proteome), including potential biomarkers for oral and systemic diseases, such as cancer and autoimmune diseases. This effort will identify all protein components in human saliva, as well as their natural variants and complexes; develop a molecular "tool box" for the isolation and functional characterization of salivary proteins; and, establish a bioinformatics environment for the dissemination of salivary proteome data to the wider scientific community. These studies will help to create the "periodic table" of the salivary proteins. These baseline data will provide a point of comparison to detect even subtle changes in the composition of saliva among people with or at risk for various diseases.

The NIH with its broad-base of expertise is well positioned to determine if there is a need to expand and accelerate research on the use of the diagnostic technologies. The NIH recognizes

the tremendous scientific opportunity and the chance to improve the early detection of breast and oral cancers as well as other diseases such as Alzheimer's disease, Sjögren's syndrome, cystic fibrosis, diabetes, osteoporosis, hepatitis and HIV.

Item

Sepsis – The Committee is aware that sepsis kills more than 215,000 Americans each year. To improve health care provider education in correctly diagnosing sepsis, the Committee urges the Director to work with outside organizations to create and implement a program to train infectious disease physicians, emergency room doctors, critical care nurses, and oncologists, especially those in rural and underserved areas, in the use of the new guidelines to identify sepsis to improve patient outcomes. The Committee further encourages the Director to work with the NIAID, NHLBI, and NCI in these provider education efforts. (p. 173)

Action taken or to be taken

Please refer to page OD-53 of this document for the NIH response on ***"Sepsis".***

Item

Spina Bifida – The Committee recognizes that Spina Bifida is the leading permanently disabling birth defect in the United States and has concerns that the NIH has not prioritized research into primary and secondary prevention of this condition. While Spina Bifida is highly preventable through proper nutrition, including appropriate folic acid consumption, too many pregnancies are still affected each year by this devastating birth defect. The Committee also acknowledges that prevention does not assist the more than 70,000 individuals living with Spina Bifida and therefore urges the NIH/NINDS/NICHD to allocate adequate and additional resources to prioritize research into primary and secondary prevention for Spina Bifida. (p. 173)

Action taken or to be taken

Please refer to page OD-46 of this document for the NIH response on "S***pina Bifida"***

Item

Spinal Muscular Atrophy – The Committee strongly urges the OD to ensure the success of the SMA Project by providing active and ongoing support from the OD as well as from other related Institute Directors, most notably NICHD. The OD is urged to take all necessary steps to ensure that the NICHD is fully engaged by expanding their scope and level of resources dedicated to SMA. (p. 173)

Action taken or to be taken

The NIH is committed to the success of the SMA Project. The project is funded and is moving quickly in its first year toward the goal of developing a therapy that can enter clinical trials within four years. The performance-based contract, awarded in 2003, accelerates all steps from recognition of a research need, through solicitation, review, and funding of targeted research subprojects. An expert steering committee, with members from academia, industry, the FDA and the NIH, actively drives the process. In its first year, the steering committee developed detailed plans for SMA drug development, and planning for gene therapy is underway. To implement these plans, the SMA project has already issued 6 solicitations for highly targeted research subprojects, and research has begun. In addition to these efforts, existing drugs are

being examined as candidates for testing against SMA in clinical trials following the rigorous approach that the NINDS devised to evaluate potential drugs for Parkinson's disease.

Central direction is fundamental to the SMA Project's innovative approach to therapy development. Thus, a single institute, the NINDS, manages the process to maintain the necessary focus, but other components of the NIH become involved as appropriate. For example, the Office or Rare Diseases in the NIH Office of the Director, as well as representatives of the FDA, participated in an NINDS led scientific workshop in September 2004 that engaged the SMA scientific community and voluntary health organizations on development of clinical trials for SMA. The NICHD is monitoring the progress of the SMA Project and will work with NINDS, as appropriate, to ensure its success. The NICHD has expertise and resources that are relevant to pediatric clinical trials and leads NIH efforts in newborn screening, which may be essential for sufficiently early intervention as SMA therapies become available. The NICHD also sponsors pediatric and basic science training programs that are available for training new investigators who have an interest in SMA, and will work with the NINDS to increase public and professional awareness of SMA.

Item

Stroke in Women – The Committee urges NIH to increase research in stroke among women of all ages, with specific attention to gender-related differences in stroke risk, and to stroke prevention interventions, acute stroke management, post-stroke recovery, long-term outcomes, and quality of care. The Committee further urges NIH to increase research into new therapies for stroke in women as well as into ways of enhancing the vascular health of all Americans. (p. 173)

Action taken or to be taken

The NIH recognizes that stroke is a significant cause of death among women, and that gender-related differences in stroke warrant close study. Research in this area is being emphasized, in particular, in the wake of recent findings from the Women's Health Initiative clinical trials, which revealed an increased risk of stroke among women who took estrogen or combined estrogen-protestin hormone therapy. A number of NINDS-funded projects are exploring issues such as the biological causes of the increased risk of stroke found in the hormone trials, a possible link between decreased estrogen in aging and stroke risk factors such as high blood pressure, and a potential neuroprotective role for the estrogens. In addition to exploring gender-specific risk factors for stroke, NINDS-funded researchers are exploring gender-specific differences in treatment effects. Specifically, the Carotid Revascularization Endarterectomy vs. Stenting Trial, which is directly comparing the efficacy of carotid endarterectomy to angioplasty/stenting, a newer less-invasive surgical meth, includes a planned analysis of gender differences in the efficacy of the two procedures.

The NHLBI supports several large-scale, population-based studies of risk factors and outcomes of stroke in women. The Framingham Heart Study, Cardiovascular Health Study, Atherosclerosis Risk in Communities Study, Strong Heart Study, and Jackson Heart Study all include prominent stroke risk assessments and show similar risk of stroke in women and men. In several of these studies, magnetic resonance imaging has demonstrated high frequencies of

"silent" stroke and other ischemic brain changes in women. The changes are strongly related to impaired cognitive and physical function, particularly in older women. How these abnormalities relate to progression of impaired cognition and dementia secondary to stroke and cerebral ischemia, and whether the declines can be prevented by interventions such as aggressive control of high blood pressure and other cardiovascular (CV) risk factors, is the subject of continued research. In addition, the NHLBI also sponsors three large clinical trials that are testing interventions to reduce stroke along with other CV diseases. All will analyze results separately by gender to determine the effect of the interventions in women. ACCORD (Action to Control Cardiovascular Risk in Diabetes) is testing the effects of intensive control of blood sugar, intensive control of blood pressure, and treatment of blood lipids with fibrate compared with the current standard of care in 10,000 adult patients with Type 2 diabetes. MOST (Mode Selection Trial in Sinus Node Dysfunction) is determining if dual-chamber rate-modulated pacing in 2,000 patients with sick sinus syndrome is superior to single-chamber pacing with respect to subsequent occurrence of either stroke or death from any cause. FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multi-vessel Disease) is evaluating, in 2,400 diabetic patients with multi-vessel coronary heart disease, the relative effectiveness of a multi-vessel percutaneous coronary intervention stenting strategy using drug-eluting stents compared with coronary artery bypass surgery.

Item

Stroke in Women -- The Committee also encourages and supports NIH's initiatives toward advancing the organization of stroke care, including post-stroke rehabilitation, and the identification of stroke treatment and research centers that would provide rapid, early, continuous 24-hour treatment to stroke victims, including the use of the clot-buster t-PA, when appropriate. Designated areas in medical facilities equipped with the resources and personnel for treating stroke would also promote the early evaluation of innovative stroke treatments. (p. 174)

Action taken or to be taken

In order to address the critical need for improved translation of stroke therapies, NINDS established the Specialized Program of Translational Research in Acute Stroke (SPOTRIAS) in September 2002; the most recent SPOTRIAS center received funding in September 2004. The SPOTRIAS centers are designed to facilitate translation of basic research findings into clinical practice, in settings where patients with acute ischemic and hemorrhagic stroke are evaluated and treated very rapidly after the onset of their symptoms. They also support a collaboration of clinical researchers from different specialties whose collective efforts will lead to new approaches to early diagnosis and treatment of acute stroke patients. Training and career development are part of the SPOTRIAS program.

One unique SPOTRIAS center is located at Suburban Hospital, a private community hospital in Bethesda, MD. In conjunction with this hospital, NINDS has established the Suburban Hospital Stroke Center, in order to increase the proportion of stroke patients treated with clot-busting drugs like t-PA and improve the overall level of care provided to stroke patients. The Center conducts translational and clinical stroke research and has created an acute stroke emergency response team (consisting of neurologists and specially trained nurses) that is continuously on call for potential stroke cases, and initiated stroke critical care pathways to ensure that stroke

patients are quickly identified, diagnosed, and treated. Following up on the success of this Center, NINDS established a second primary stroke center at the Washington Hospital Center (WHC) – a private community hospital that serves the predominantly minority population of Washington DC – in 2004. More than 75 percent of stroke patients at WHC are either African American or Hispanic, populations that have a disproportionately high rate of stroke mortality. As of October 2004, an NIH Stroke Team is on call at WHC 24 hours a day, 7 days a week to guide treatment of all stroke patients at the hospital, providing investigational treatments and risk factor education. In addition, construction has begun on a cutting-edge imaging facility which is due to open at WHC in 2005. This facility will enable clinicians to improve their diagnostic accuracy for stroke patients, and the Center to enhance its stroke research program development and testing of new stroke therapies.

As a complement to these efforts, in December 2002, NINDS, the National Stroke Association, and the American Stroke Association sponsored a large workshop on the delivery of acute stroke treatment. The goal of this meeting was to bring physicians, other health care professionals, and scientists together to discuss how communities can improve access to treatments for stroke patients.

Item

Tuberous Sclerosis Complex —In its report accompanying the fiscal year 2004 appropriations, the Committee called upon the Office of the Director to formulate an NIH-wide research agenda on tuberous sclerosis complex, and to report back to the Committee on this effort. While a research agenda was developed, the Committee is disappointed by the failure to act upon it. The report to the Committee cited research studies that were carried out several years ago or which only generally relate to TSC, and failed to establish a mechanism to coordinate research activities across several Institutes. The Committee strongly urges the OD to establish such coordinating mechanism as soon as possible, and to undertake TSC-specific research. (p. 174)

Action taken or to be taken

The National Institute of Neurological Disorders and Stroke (NINDS) formed a trans-NIH tuberous sclerosis (TSC) coordinating committee, which met for the first time in April 2004, to coordinate research activity across Institutes. This committee includes representatives from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), National Heart, Lung, and Blood Institute (NHLBI), National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS), National Cancer Institute (NCI), (National Institute of Mental Health (NIMH), National Institute of Child Health and Human Development (NICHD), and the NIH Office of Rare Diseases. Members of the coordinating committee are currently working together to develop a program announcement to promote TSC therapy development and otherwise implement the objectives outlined in the TSC research plan.

The NIH supports a variety of research focused specifically on TSC. Many of the projects cited in the report accompanying the FY 2004 appropriations continue to receive support, although the grants may initially have been awarded several years ago. These ongoing projects include studies of the relationship between TSC mutations and the development of neurological abnormalities, elucidation of the molecular pathway through which the TSC genes control cell growth and

proliferation, and the development of gene therapy strategies to control tumor growth in animal models of TSC---all of these projects are directly related to TSC, and both molecular studies and studies of animal models will be crucial for developing therapies for TSC patients. The NIH also funded several new studies in FY 2004, including a preclinical study to test whether the FDA-approved drug rapamycin and two newer analogs can improve survival, development, and seizure frequency, and decrease brain pathology in two different mouse models of TSC; a study to determine how the cellular environment contributes to the growth of TSC tumors; and several projects that are dissecting the molecular pathways in which the TSC gene products operate.

Item

Vascular Biology – The Committee recognizes the importance of advancing research in the field of vascular biology, the study of blood and blood vessels and their interactions. Not only is the maintenance of the blood supply critical to the functioning of all organs of the body, understanding the mechanisms and treatment of diseases that interrupt the blood supply is relevant to all organ systems and their disorders. Research into vascular biology can provide the scientific basis for new therapies to prevent thrombosis; therapies that are important to the prevention and control of heart disease, stroke, recurrent fetal loss, and complications associated with sickle cell anemia and diabetes; and therapies related to the interruption of the blood supply to tumors and cancers. Because of the cross-cutting aspects of this research, the Committee urges the NIH Director to develop a comprehensive NIH-wide approach to identify and pursue research opportunities in this field. (p. 174)

Action taken or to be taken

Please refer to page OD-44 of this document for the NIH response on "**V*ascular Biology*".**

FY 2005 Conference Committee Report Language (C. Rpt. 108-792)

Item

NIH Library of Medicine infrastructure - The Committee continues to strongly support the work of the National Library of Medicine, the largest medical library in the world and the leader in digitized medical information resources. Previously, the Committee has taken steps to ensure that adequate funding was available for the architectural planning and design of a new NLM building to house the National Center for Biotechnology Information and other activities related to digital information development. With the preliminary work complete, the Committee urges the Secretary to consider the commitment of necessary resources to begin construction of new physical facilities for the NLM to enable it to keep pace with the rapid increase in medical publishing and biotechnology information research and development. (p. 145)

Action taken or to be taken

The NIH, supported by the recommendations of its Facilities Working Group, has included it in the overall NIH strategic facilities plan as a long term proposed project.

Item

Multidisciplinary research – The conferees are aware that recent advances in multidisciplinary research combining biomaterials, cell biology, computer modeling, micro-machining and nanotechnology have made it possible to produce fully functioning replacement kidneys and liver tissue. The multidisciplinary tissue engineering research efforts have resulted in positive results to date in the development of a compact, wearable continuous kidney dialysis system that will greatly improve the lives of patients. The conferees encourage the Director of NIH to pursue research initiatives on the development of tissue-engineered compact, wearable, continuous kidney dialysis and liver support systems. (p. 1177)

Action Taken or to be Taken

Liver failure and kidney failure are serious problems that affect tens of thousands of people in the United States each year. In people with acute liver failure due to toxic agents such as viruses or drugs, the only effective therapy available is liver transplantation, a procedure with a long waiting list. An artificial or bioartificial liver assist device could be used to sustain these patients and serve as a bridge to liver transplantation. A new form of therapy in development, the bioartificial liver (BAL) could provide detoxification and synthetic activity to patients with liver failure prior to transplantation, until recovery of the native liver, or as a chronic supportive therapy. The BAL operates extracorporeally—outside the body—like kidney hemodialysis therapy, but unlike hemodialysis contains metabolically active liver cells (i.e., hepatocytes) that provide liver functions to the patient. The NIH is supporting research to address biological, mechanical, and bioengineering issues that could lead to improved BAL. Several studies seek to optimize the preservation, viability, and functionality of human and animal hepatocytes in the environment of the BAL. Studies to determine the minimum cell mass to support a patient, critical hepatocyte functions for patient survival, and the impact of the BAL treatment on the immune system and on subsequent transplantation are also pursued. Other studies are developing biocompatible substrates and scaffolds that preserve hepatocyte function while improving their bioengineering properties to increase the efficiency of the BAL. In the recently completed *Trans-NIH Action Plan for Liver Disease Research*, leaders in this field from the NIH, external research, and health care communities identified the development of a hepatic assist device or bioartificial liver to support patients with acute liver failure as an important research goal to pursue over the next decade with NIH support (http://www.niddk.nih.gov/fund/divisions/ddn/ldrb/ldrb_action_plan.htm). The *Action Plan* emphasizes the critical importance of forming multidisciplinary collaborations between basic and clinical researchers in order to achieve these goals.

The kidney filters wastes from blood and regulates other functions of the body. When kidneys fail—a condition known as end-stage renal disease—treatment is necessary to replace the function of healthy kidneys and to survive. Treatment choices are hemodialysis, peritoneal dialysis, and kidney transplantation. The NIH has been working with investigators developing approaches to hemodialysis and peritoneal dialysis therapy that use innovative methods and materials, and is encouraging research using both the Small Business Innovation Research (SBIR) program and standard grant mechanisms. If feasibility issues can be resolved, and safety

can be established, we anticipate these approaches may potentially allow the development of ambulatory devices that increase patient mobility and diminish the impact of end-stage renal disease on the quality of life.

Item

***[Impact of omega-3 fatty acids]* –** The conferees acknowledge the positive conclusions of the evidence-based review recently completed by the Office of Dietary Supplements on the potential benefits of omega-3 fatty acids in significantly lowering the risks of cardiovascular disease, especially coronary heart disease. The conferees urge NIH to undertake the design and planning of the recommended clinical trials needed to provide conclusive evidence regarding the potential of omega-3 fatty acids in reducing cardiovascular morbidity and mortality in the general U.S. population. (p. 1178)

Action taken or to be taken

The evidence-based review on omega-3-fatty acids and cardiovascular disease, recently completed by the Office of Dietary Supplements, has been considered by a ODS/NHLBI working group consisting of nutritional and clinical trial experts. The ODS and NHLBI are evaluating the working group's recommendations regarding future research, including potential clinical trials to examine the effects of omega-3-fatty acids on cardiovascular disease. A brief report of the ODS/NHLBI working group meeting on omega-3 fatty acids is currently available on the NHLBI website (http://www.nhlbi.nih.gov/meetings/workshops/omega3-summary.htm), and a longer report is being prepared for posting.

Item

Psychosocial care for cancer patients -- The conferees are concerned about the absence of mechanisms to ensure the delivery of necessary psychosocial care to individuals with cancer and their family members. The conference agreement provides $1,000,000 for the Secretary, working in collaboration with the Institute of Medicine and relevant government agencies and non-profit entities, to study the delivery of psychosocial services to cancer patients and their families in the community setting. Specifically, the report should include an analysis of: (1) the capacity of the current mental health and oncology provider system to deliver such care and the anticipated resources required nationwide; (2) available training programs for professionals providing psychosocial and mental health services; and (3) existing barriers to access to such care. The Secretary is encouraged to issue recommendations to address these issues. (p. 1204)

Action taken or to be taken

The extent to which the current service delivery system is capable of providing psychosocial services to cancer patients and their families is presently unknown. Needed is an assessment of cancer patient and family mental health needs, mental health and oncology provider resources, factors influencing patient and family access to these resources, and psychosocial training programs available to professionals providing care to cancer patients and their families.

The Office of the Secretary has delegated responsibility for this activity to the NIH. The Office of Behavioral and Social Sciences Research, within the NIH Office of the Director, will coordinate a meeting of staff from several NIH institutes and centers, the Substance Abuse and Mental Health

Services Administration and the Agency for Healthcare Research and Quality, to clarify research requirements. The Institute of Medicine will be invited to propose a research study, with likely FY 2005 funding.